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(54) Processes for preparing optically active alcohols and optically active amines

Verfahren zur Herstellung von optisch aktiven Alkoholen und von optischen aktiven Aminen

Procédés pour la préparation d'alcools optiquement actifs et d'amines optiquement actives

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(56) References cited:
EP-A- 0 485 069 **EP-A- 0 641 786**

- **DATABASE WPI Section Ch, Week 9528 Derwent Publications Ltd., London, GB; Class B03, AN 95-209417 XP002022387 & JP 07 109 231 A (SUMITOMO CHEM CO LTD) , 25 April 1995**
- **TETRAHEDRON LETTERS, vol. 29, no. 2, 1988, OXFORD GB, pages 223-224, XP002022386 Y. SAKITO ET AL.: "Asymmetric reductions of oxime ethers. Distinction of anti and syn isomers leading to enantiomeric amines."**
- **SHINICHI ITSUNO ET AL.: "Assymetric reduction of ketoxim O-alkyl ethers with NaBH4/lewis acid", J. CHEM. SOC., PERKIN TRANSACTIONS 1, , 17. April 1989, vol. , no. 8, pages 1548 to 1549**
- **SHINICHI ITSUNO ET AL.: "Assymetric synthesis using chirally modified borohydrides PART 3.", J. CHEM. SOC., PERKIN TRANSACTIONS 1, , 01. January 1985, vol. , no. , pages 2039 to 2044**

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Description

[0001] The present invention relates to a process for preparing an optically active alcohol and a process for preparing an optically active amine.

[0002] As a process for preparing an optically active alcohol, for example, there is known a process comprising reacting an optically active β-aminoalcohol and a borane in an amount of two moles per one mole of said aminoalcohol, and then reacting a prochiral ketone in an amount of 0.8 mole per one mole of said aminoalcohol with a reaction product (see, for example, J. Chem. Soc. PERKIN TRANS. I., 2039 (1985)).

[0003] However, this process has a drawback that a large amount of the expensive borane should be used.

[0004] To solve such drawback, JP-A-7-109231 discloses a process for preparing an optically active alcohol using a metal borohydride which is cheap and easily available in an industrial scale, that is, a process comprising reacting a mixture of a 2-substituted oxazaborolidine having substituents on a boron atom and a metal borohydride with an acid, and then reacting a prochiral ketone with a reaction product to obtain an optically active alcohol. But, an optical purity of the produced optically active alcohol is unsatisfactory, and further improvement of the process has been desired.

[0005] As a process for preparing an optically active amine, there is proposed a process comprising reacting an optically active β-aminoalcohol with a borane, and then reacting a syn or anti-form of an oxime derivative with a reaction product, whereby an optically active amine having a desired absolute configuration is prepared (see JP-A-63-99041 and Tetrahedron Lett., 29223 (1988).

[0006] However, this process has a drawback that a large amoutn of an expensive borane should be used.

[0007] To solve such drawback, JP-A-2-311446 and JP-A-5-9158 disclose a process for preparing an optically active amine using a metal borohydride which is cheap and easily available in an industrial scale, that is, a process comprising reacting an optically active β-aminoalcohol with a metal borohydride and an acid, and then reacting an oxime derivative with a reaction product.

[0008] J.Chem. Soc. Perkin Trans., 1, 1989, pp 1548-49 investigates on hydride agents formed by combining Lewis acids with $NaBH_4$ in the reduction of ketoxime O-alkyl ethers to the corresponding optically active primary amines in the presence of chiral amino alcohols.

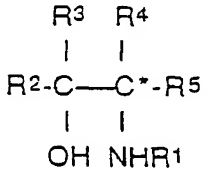
[0009] An object of the present invention is to provide a process for preparing an optically active alcohol having an increased optical purity effectively even in an industrial scale while reducing an amount of a used metal borohydride or boron hydride as a hydrogen source.

[0010] Another object of the present invention is to provide a process for preparing an optically active amine having an increased optical purity effectively even in an industrial scale while reducing an amount of a used metal borohydride or boron hydride as a hydrogen source.

[0011] According to a first aspect of the present invention, there is provided a process for preparing an optically active alcohol comprising reacting a prochiral ketone which corresponds to the optically active alcohol and an acid with a mixture which comprises

(1) a boron-containing compound selected from the group consisting of

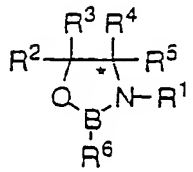
i) a borane compound which is obtained from an optically active β-aminoalcohol of the formula (I):



(I)

wherein R^1 is a hydrogen atom, a lower alkyl group or an aralkyl group which may have at least one substituent, R^2, R^3, R^4 and R^5 represent independently each other a hydrogen atom, a lower alkyl group, an aryl group which may have at least one substituent, or an aralkyl group which may have a substituent, provided that R^4 and R^5 are different, that R^1 and R^5 may together form a lower alkylene group, or that R^3 and R^4 may together form a lower alkylene group which may have optionally a substituent or with which a benzene ring is condensed, and * stands for an asymmetric carbon atom, and a boron hydride; or obtained from said optically active β-aminoalcohol (I), a metal borohydride and an acid wherein the amount of the optically active β-aminoalcohol (I) is from 0.005 to 0.5 mole per mole of the prochiral ketone, and

ii) an optically active oxazaborolidine of the formula (II):



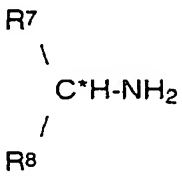
(II)

wherein R^1, R^2, R^3, R^4, R^5 and * are the same as defined above, and R^6 is a hydrogen atom, a halogen atom, an alkyl group which may be substituted by at least one halogen atom, an aryl group which may have at least one substituent or an aralkyl group which may have at least one substituent,

and

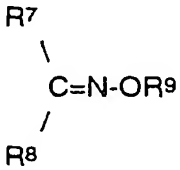
(2) a metal borohydride.

[0012] According to a second aspect of the present invention, there is provided a process for preparing an optically active amine of the formula:(III):



(III)

wherein R^7 and R^8 are different and represent an alkyl group which may have at least one substituent, an aryl group which may have at least one substituent or an aralkyl group which may have at least one substituent, or R^7 and R^8 form, together with the carbon atom bonded to the amino group, a ring or condensed ring which may have a hetero atom, and * is the same as defined above comprising reacting an oxime derivative of the formula (IV):



(IV)

wherein R^7 and R^8 are the same as defined above, and R^9 is an alkyl group, an aralkyl group or an alkyl-substituted silyl group and an acid with a mixture which comprises

(1) a boron-containing compound selected from the group consisting of

i) a borane compound which is obtained from an optically active β-aminoalcohol of the formula (I) and a boron hydride, or obtained from said optically active β-aminoalcohol (I), a metal borohydride and an acid wherein the amount of the optically active β-aminoalcohol (I) is from 0.01 to 0.9 mole per mole of the oxime derivative (IV), and

ii) an optically active oxazaborolidine of the formula (II) and (2) a metal borohydride.

[0013] The oxime derivative (IV) may be a syn-form, an anti-form or a mixture thereof which is rich in one of them.

Preparation of a mixture of a borane compound and metal borohydride

[0014] R^1 in the optically active β-aminoalcohol of the formula (I) is a hydrogen atom, a straight or branched lower alkyl group having usually 1 to 8 carbon atom, preferably 1 to 5 carbon atoms (e.g. methyl, ethyl, n-propyl, isopropyl,

n-butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, etc.), or an aralkyl group having usually 7 to 15 carbon atom, preferably 7 to 12 carbon atoms (e.g. benzyl, phenethyl, methylbenzyl, etc.) which may be substituted with a lower (C_1-C_5) alkyl or alkoxy group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, etc.).

[0015] R^2, R^3, R^4 and R^5 represent independently each other a hydrogen atom, a lower alkyl group having usually 1 to 8 carbon atom, preferably 1 to 5 carbon atoms (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, etc.), an aryl group having 6 to 12 carbon atoms, preferably 6 to 11 carbon atoms (e.g. phenyl, 1-naphthyl, 2-naphthyl, etc.), or an aralkyl group having usually 7 to 12 carbon atoms (e.g. benzyl, phenethyl, methylbenzyl, etc.). The aryl or aralkyl group may be substituted with a lower alkyl or alkoxy group which may be the same as exemplified above. R^4 and R^5 are not the same. R^1 and R^5 may together form a lower alkylene group such as methylene, dimethylene, trimethylene, tetramethylene, etc. R^3 and R^4 may together form a lower alkylene group which may have optionally a substituent or with which a benzene ring is condensed, such as trimethylene, tetramethylene, pentamethylene, o-phenylenemethylene, o-phenylenedimethylene, etc.

[0016] Specific examples of the optically active β-aminoalcohol (I) are optically active norephedrine, ephedrine, 2-amino-1-(2,5-dimethylphenyl)-1-propanol, 2-amino-1-(2,5-dimethoxyphenyl)-1-propanol, 2-amino-1-(2,5-diethoxyphenyl)-1-propanol, 2-amino-1-(2,5-dipropoxyphenyl)-1-propanol, 2-amino-1-(2-methoxyphenyl)-1-propanol, 2-amino-1-(2-ethoxyphenyl)-1-propanol, 2-amino-1-(2-propoxyphenyl)-1-propanol, 2-amino-1-(2-methylphenyl)-1-propanol, 2-amino-1-(2-methoxy-5-methylphenyl)-1-propanol, 2-amino-1-(4-methoxy-2-methylphenyl)-1-propanol, 2-amino-1-(2-ethoxy-5-methylphenyl)-1-propanol, 2-amino-1-(2,4-dimethylphenyl)-1-propanol, 2-amino-1-(2,4,6-trimethylphenyl)-1-propanol, 2-amino-1-(1-naphthyl)-1-propanol, 2-amino-1-(2-naphthyl)-1-propanol, 2-amino-1,2-diphenylethanol, 2-amino-1,1-diphenyl-1-propanol, 2-amino-1,1-diphenyl-3-methyl-1-butanol, 2-amino-1,1-diphenyl-4-methyl-1-propanol, 2-amino-1,1-diphenyl-1-butanol, 2-amino-1,1,3-triphenyl-1-propanol, 2-amino-1,1,2-triphenyl-1-ethanol, 2-amino-3-methyl-1-butanol, 2-amino-4-methyl-1-pentanol, 2-amino-1-propanol, 2-amino-3-phenyl-1-propanol, 2-amino-2-phenyl-1-ethanol, etc., and their N-lower alkyl or N-aralkyl derivatives; 2-pyrrolidinemethanol, α,α-diphenyl-2-pyrrolidinemethanol, 2-piperidinemethanol, α,α-diphenyl-2-piperidinemethanol, 2-aziridinemethanol, α,α-diphenyl-2-aziridinemethanol, 2-azetizinemethanol, α,α-diphenyl-2-azetizinemethanol, 2-aminocyclopentan-1-ol, 2-aminocyclohexan-1-ol, 1-aminoindan-2-ol, and so on.

[0017] Examples of the boron hydride are diborane, boranetetrahydrofuran complex, borane-dioxane complex, boranedimethylsulfide complex, borane-thioxane complex, and so on.

[0018] Examples of the metal borohydride are lithium borohydride, sodium borohydride, potassium borohydride, zinc borohydride, and so on. Among them, sodium borohydride is preferred.

[0019] The metal borohydride used in the preparation of the borane compound and that used in the reduction of the prochiral ketone or the oxime derivative (IV) are usually the same, while they may be different.

[0020] Examples of the acid are Brønsted acids such as sulfuric acid, acetic acid, phosphoric acid, methanesulfonic acid, p-toluenesulfonic acid, hydrogen chloride, etc.; and Lewis acids such as zinc chloride, boron trifluoride, aluminum chloride, aluminum bromide, titanium tetrachloride, tin tetrachloride, tin trichloride, iodine, etc.

[0021] The acid used in the preparation of the borane compound and that used in the reduction of the prochiral ketone or the oxime derivative (IV) are usually the same, while they may be different.

[0022] The preparation of the borane compound and the reduction of the prochiral ketone or the oxime derivative (IV) are usually performed in the presence of a solvent. The solvent used in the preparation of the borane compound and that used in the reduction of the prochiral ketone or the oxime derivative (IV) are usually the same, while they may be different.

[0023] Examples of the solvent are ethers (e.g. dioxane, 1,3-dioxolane, tetrahydrofuran, diglyme, etc.), sulfides (e.g. dimethylsulfide, diethylsulfide, etc.), and mixtures thereof, and mixtures of the above solvent and a hydrocarbon (e.g. benzene, toluene, xylene, chlorobenzene, 1,2-dichloroethane, etc.).

[0024] An amount of the solvent is usually from 1 to 50 times the weight of the prochiral ketone or the oxime derivative (IV).

[0025] In the preparation of the borane compound, in general, the boron hydride is added to the mixture of the optically active β-aminoalcohol (I) and the solvent, or the acid is added to the mixture of the optically active β-aminoalcohol (I), the metal borohydride and the solvent. The boron hydride or the acid may be used as a mixture in the solvent.

[0026] In general, the boron hydride or the metal borohydride is used in an amount of 0.8 to 2 moles in terms of the boron atom per one mole of the optically active β-aminoalcohol (I). When the metal borohydride is used, it may be added, at this stage, in an amount sufficient for performing the reaction with the optically active β-aminoalcohol (I) and also the reduction of the prochiral ketone or the oxime derivative (IV). The metal borohydride is more preferably used than the boron hydride.

[0027] The acid is used usually in an amount of 0.8 to 2.1 equivalents of the optically active β-aminoalcohol (I).

[0028] In general, an amount of the metal borohydride which contributes to the synthesis of the borane compound is determined by the amount of the acid. Theoretically, an excessive portion of the metal borohydride in relation to the

acid will form a mixture with the borane compound.

[0029] A temperature at which the boron hydride is added is usually from -20 to +100°C, preferably from 0 to 80°C. After the addition of the boron hydride, the reaction mixture is preferably stirred at the same temperature for 0.1 to 20 hours.

[0030] A temperature at which the acid is added is usually from -20 to +100°C, preferably from 0 to 80°C. After the addition of the acid, the reaction mixture is preferably stirred at the same temperature for 0.1 to 10 hours.

[0031] In the reduction of the prochiral ketone, an amount of the optically active β-aminoalcohol (I) is from 0.005 to 0.5 mole, preferably from 0.01 to 0.4 mole per one mole of the prochiral ketone. In the reduction of the oxime derivative (IV), an amount of the optically active β-aminoalcohol (I) is from 0.01 to 0.9 mole, preferably 0.03 to 0.9 mole per one mole of the oxime derivative (IV).

[0032] In a case where the metal borohydride is added in the preparation step of the borane compound in an amount sufficient for performing the reaction with the optically active β-aminoalcohol (I) and also the reduction of the prochiral ketone or the oxime derivative (IV), the mixture of the borane compound and the metal borohydride is obtained, while, in other case, such mixture is obtained by the addition of the metal borohydride to the resulting borane compound.

[0033] When the metal borohydride is additionally added, an amount of the metal borohydride in the mixture with the borane compound is usually from 0.3 to 3 moles, preferably from 0.5 to 2 moles in terms of the boron atom per one mole of the prochiral ketone in the case of the reduction of the prochiral ketone. The reaction proceeds sufficiently when this amount is from 0.5 to 1 mole. In the case of the reduction of the oxime derivative, the additional amount of the metal borohydride is usually from 0.5 to 2.1 moles, preferably from 0.8 to 1.5 moles in terms of the boron atom per one mole of the oxime derivative (IV).

Preparation of a mixture of a optically active oxazaborolidine (II) and a metal borohydride

[0034] Examples of the alkyl, aralkyl and aryl groups for R^1, R^2, R^3, R^4 and R^5, and examples of the alkylene group formed from R^1 and R^5 or R^3 and R^4 in the optically active oxazaborolidine (II) are the same as those exemplified in connection with the optically active β-aminoalcohol (I).

[0035] Examples of the lower alkyl group for R^6 are the same as those for R^2 and so on, that is, an alkyl group having usually 1 to 8 carbon atoms which may be substituted with 1 to 6 halogen atoms (e.g. hexyl, cyclohexyl, heptyl, 2-ethylhexyl, octyl, 1-chloroethyl, 1-bromoethyl, 1-fluoroethyl, 2-fluoroethyl, 3-chloropropyl, 3,3,3-trifluoropropyl. Examples of the aryl group are an aryl group having usually 6 to 12 carbon atoms, preferably 6 to 10 carbon atoms (e.g. phenyl, 1-naphthyl, 2-naphthyl, etc.), an aryl group substituted with at least one alkyl group having usually 1 to 8 carbon atoms (e.g. o-, m- or p-methylphenyl, o-, m- or p-ethylphenyl, o-, m- or p-butylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethylphenyl, etc.), an aryl group substituted with at least one alkoxy group having usually 1 to 8 carbon atoms (e.g. o-, m- or p-methoxyphenyl, o-, m- or p- ethoxyphenyl, o-, m- or p-propoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethoxyphenyl, etc.), an aryl group substituted with at least one halogen atom (e.g. o-, m- or p-chlorophenyl, o-, m- or p-bromophenyl, o-, m- or p-fluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6- or 3,4,5- trifluorophenyl, etc.), an aryl group substituted with at least one halogen atom and at least one alkyl group (e.g. 4-bromo-3,5-dimethylphenyl, 4-bromo-2,6-dimethylphenyl, 4-fluoro-3,5-dimethylphenyl, etc.), an aryl group substituted with at least one halogen atom and at least one alkoxy group (e.g. 2-chloro-5-methoxyphenyl, 2-bromo-5-methoxyphenyl, 2-fluoro-5-methoxyphenyl, 3-bromo-5-methoxyphenyl, 4-ethoxy-2,3-difluorophenyl, etc.), and an aryl group substituted with a halogenated alkyl group (e.g. 2-(chloromethyl)phenyl, 2-(bromomethyl)phenyl, 2-(fluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, o-, m- or p-(1-chloroethyl)phenyl, o-, m- or p-(1-bromoethyl)phenyl, o-, m- or p-(3-chloropropyl)phenyl, 2-bromomethyl-6-methylphenyl, etc.). Examples of the aralkyl group are an aralkyl group having usually 7 to 12 carbon atoms, preferably 7 to 10 carbon atoms (e.g. benzyl, etc.), an aralkyl group substituted with at least one alkyl or alkoxy group having 8 to 13 carbon atoms (e.g. o-, m- or p-tolylmethyl, o-, m- or p-ethylbenzyl, o-, m- or p-methoxybenzyl, o-, m- or p-ethoxybenzyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethylbenzyl, (2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethylphenyl)ethylalkyl. Examples of the halogen atom are fluorine, chlorine and bromine.

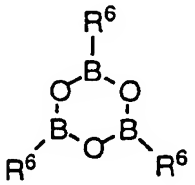
[0036] Specific examples of the optically active oxazaborolidine (II) are optically active 1,3,2-(4-methyl-5-phenyl) oxazaborolidine, 1,3,2-(2,4-dimethyl-5-phenyl)oxazaborolidine, 1,3,2-(2-ethyl-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-propyl-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-butyl-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(4-methyl-2,5-diphenyl)oxazaborolidine, 1,3,2-(2-(o-fluorophenyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-(m-fluorophenyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-(p-fluorophenyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-(2,4-difluorophenyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-(2,5-difluorophenyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-(2,6-difluorophenyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-(2-chlorophenyl)-4-methyl-5-phenyl) oxazaborolidine, 1,3,2-(2-(3-chlorophenyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-(2,3-dichlorophenyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-(2,6-dichlorophenyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-(3,5-dichlorophenyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-(o-methoxyphenyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-(m-methoxyphenyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-(p-methoxyphenyl)-4-methyl-5-phenyl)ox-

azaborolidine, 1,3,2-(2-(2,5-dimethoxyphenyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-(o-tolyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-(m-tolyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-(p-tolyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(2-(2,5-dimethylphenyl)-4-methyl-5-phenyl)oxazaborolidine, 1,3,2-(4,5-diphenyl)oxazaborolidine, 1,3,2-(2-methyl-4,5-diphenyl)oxazaborolidine, 1,3,2-(2-methyl-4,5-di(2-naphthyl))oxazaborolidine, 1,3,2-(4,5-di(2-naphthyl))oxazaborolidine, 1,3,2-(2-methyl-4-(2-methylpropyl)-5-phenyl)oxazaborolidine, 1,3,2-(4-(2-methylpropyl)-5-phenyl)oxazaborolidine, 1,3,2-(2-methyl-4-(1-methylpropyl)-5-phenyl)oxazaborolidine, 1,3,2-(4-(1-methylpropyl)-5-phenyl)oxazaborolidine, 1,3,2-(2-methyl-4-(1-methylethyl)-5-phenyl)oxazaborolidine, 1,3,2-(4-(1-methylethyl)-5-phenyl)oxazaborolidine, 1,3,2-(2-methyl-4-(1,1-dimethylethyl)-5-phenyl)oxazaborolidine, 1,3,2-(4-(1,1-dimethylethyl)-5-phenyl)oxazaborolidine, 1,3,2-(2-methyl-4-(phenylmethyl)-5-phenyl)oxazaborolidine, 1,3,2-(4-(phenylmethyl)-5-phenyl)oxazaborolidine, 1,3,2-(2-methyl-4-(phenyl-5-(p-tolyl))oxazaborolidine, 1,3,2-(4-(phenyl-5-(p-tolyl))oxazaborolidine, 1,3,2-(2,4-dimethyl-5-(2,5-dimethylphenyl))oxazaborolidine, 1,3,2-(4-methyl-5-(2,5-dimethylphenyl))oxazaborolidine, 1,3,2-(2,4-dimethyl-5-(2,5-dimethoxyphenyl))oxazaborolidine, 1,3,2-(4-methyl-5-(2,5-dimethoxyphenyl))oxazaborolidine, 1,3,2-(2-methyl-4-phenyl)oxazaborolidine, 1,3,2-(4-phenyl)oxazaborolidine, 1,3,2-(2,4-diphenyl)oxazaborolidine, 1,3,2-(2,4-dimethyl)oxazaborolidine, 1,3,2-(4-methyl)oxazaborolidine, 1,3,2-(4-ethyl)oxazaborolidine, 1,3,2-(2-methyl-4-ethyl)oxazaborolidine, 1,3,2-(4-propyl)oxazaborolidine, 1,3,2-(2-methyl-4-propyl)oxazaborolidine, 1,3,2-(4-isopropyl)oxazaborolidine, 1,3,2-(2-methyl-4-isopropyl)oxazaborolidine, 1,3,2-(2-methyl-4-(1-methylpropyl))oxazaborolidine, 1,3,2-(4-(1-methylpropyl))oxazaborolidine, 1,3,2-(2-methyl-4-(2-methylpropyl))oxazaborolidine, 1,3,2-(4-(2-methylpropyl))oxazaborolidine, 1,3,2-(2-methyl-4-(tert.-butyl))oxazaborolidine, 1,3,2-(4-(tert.-butyl))oxazaborolidine, 1,3,2-(2-methyl-4,5,5-triphenyl)oxazaborolidine, 1,3,2-(4,5,5-triphenyl)oxazaborolidine, 1,3,2-(4-benzyl)oxazaborolidine, 1,3,2-(2-methyl-4-benzyl)oxazaborolidine, 1,3,2-(2-methyl-4-benzyl-5,5-diphenyl)oxazaborolidine, 1,3,2-(4-benzyl-5,5-diphenyl)oxazaborolidine, 1,3,2-(4-methyl-5,5-diphenyl)oxazaborolidine, 1,3,2-(4-isopropyl-5,5-diphenyl)oxazaborolidine, 1,3,2-(4-isobutyl-5,5-diphenyl)oxazaborolidine, 1,3,2-(2,4-dimethyl-5,5-diphenyl)oxazaborolidine, 1,3,2-(4-isopropyl-2-methyl-5,5-diphenyl)oxazaborolidine, 1,3,2-(4-isobutyl-2-methyl-5,5-diphenyl)oxazaborolidine, 1,3,2-(2,5,5-trimethyl-4-(tert.-butyl))oxazaborolidine, 1,3,2-(5,5-dimethyl-4-(tert.-butyl))oxazaborolidine, 1,3,2-(2,4-dimethyl-5,5-di(o-methylphenyl))oxazaborolidine, 1,3,2-(4-methyl-5,5-di(o-methylphenyl))oxazaborolidine, 1,3,2-(2,4-dimethyl-5,5-dibenzyl)oxazaborolidine, 1,3,2-(4-methyl-5,5-dibenzyl)oxazaborolidine, 1,3,2-(2,4-dimethyl-5,5-di(p-methoxyphenyl)oxazaborolidine, 1,3,2-(4-methyl-5,5-di(p-methoxyphenyl)oxazaborolidine, 3,4-propano-1,3,2-oxazaborolidine, 5,5-diphenyl-3,4-propano-1,3,2-oxazaborolidine, 2-methyl-5,5-diphenyl-3,4-propano-1,3,2-oxazaborolidine, 2-methyl-3,4-propano-1,3,2-oxazaborolidine, 2-ethyl-3,4-propano-1,3,2-oxazaborolidine, 5,5-diphenyl-3,4-ethano-2-methyl-1,3,2-oxazaborolidine, 3,4-butano-5,5-di(p-tolyl)-2-methyl-1,3,2-oxazaborolidine, and so on.

[0037] The optically active oxazaborolidine (II) can be prepared by reacting the optically active β-aminoalcohol (I) with a boronic acid of the formula (V):

$$R^6\text{-}B(OH)_2 \qquad (V)$$

wherein R^6 is the same as define above, or with a boroxine derivative of the formula (VI):



(VI)

wherein R^6 is the same as defined above.

[0038] Examples of the groups for R^6 in the formulas (V) and (IV) are the same as those exemplified above.

[0039] Specific examples of the boronic acid (V) are boronic acid, methylboronic acid, ethylboronic acid, propylboronic acid, butylboronic acid, pentylboronic acid, hexylboronic acid, phenylboronic acid, α,β-naphthylboronic acid, o-, m- or p-methylphenylboronic acid, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethylphenylboronic acid, mesitylboronic acid, o-, m- or p-fluorophenylboronic acid, o-, m- or p-chlorophenylboronic acid, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenylboronic acid, benzylboronic acid, o-, m- or p-tolylmethylboronic acid, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5- dimethylbenzylboronic acid, and so on.

[0040] Specific examples of the boroxine derivative (VI) are trimethylboroxine, triethylboroxine, tripropylboroxine,

tributylboroxine, triisobutylboroxine, tripentylboroxine, trihexylboroxine, trioctylboroxine, tris(1-methylethyl)boroxine, tris(1,1-dimethylethyl)boroxine, tris(1-methylpropyl)boroxine, tris(1,1-diethylpropyl)boroxine, tris(1-chloroethyl)boroxine, tris(3-chloropropyl)boroxine, tris(3,3,3-trifluoropropyl)boroxine, triphenylboroxine, tris(2-methylphenyl)boroxine, tris(3-methylphenyl)boroxine, tris(4-methylphenyl)boroxine, tris(2-ethylphenyl)boroxine, tris(3-ethylphenyl)boroxine, tris(4-ethylphenyl)boroxine, tris(2,3-dimethylphenyl)boroxine, tris(2,4-dimethylphenyl)boroxine, tris(2,5-dimethylphenyl)boroxine, tris(2,6-dimethylphenl)boroxine, tris-(3,4-dimethylphenyl)boroxine, tris(3,5-dimethylphenyl)boroxine, tris (2-methoxyphenyl)boroxine, tris(3-methoxyphenyl)boroxine, tris(4-methoxyphenyl)boroxine, tris(2-ethoxyphenyl) boroxine, tris(2-propoxyphenyl)boroxine, tris(2-chlorophenyl)boroxine, tris(3-chlorophenyl)boroxine, tris(4-chlorophenyl)boroxine, tris(3-bromophenyl)boroxine, tris(3-fluorophenyl)boroxine, tris(4-chlorophenyl)boroxine, tris (4-bromophenyl)boroxine, tris(4-fluorophenyl)boroxine, tris(2,3-difluorophenyl)boroxine, tris(2,4-difluorophenyl)boroxine, tris(2,5-difluorophenyl)boroxine, tris(2,6-difluorophenyl)boroxine, tris(3,4-difluorophenyl)boroxine, tris(3,5-difluorophenyl)boroxine, tris(4-bromo-2,6-dimethylphenyl)boroxine, tris(4-bromo-3,5-dimethylphenyl)boroxine, tris(4-bromo-3,6-dimethylphenyl)boroxine, tris(2-chloro-5-methoxyphenyl)boroxine, tris(2-bromo-5-methoxyphenyl)boroxine, tris (2-fluoro-5-methoxyphenyl)boroxine, tris(5-bromo-2-methoxyphenyl)boroxine, tris(4-chloro-3-methoxyphenyl)boroxine, tris(4-ethoxy-2,3-difluorophenyl)boroxine, tris(2-(chloromethyl)phenyl)boroxine, tris(2-(bromomethyl)phenyl) boroxine, tris(4-(bromomethyl)phenyl)boroxine, tris(o-(1-bromoethyl)phenyl)boroxine, tris(m-(1-bromoethyl)phenyl) boroxine, tris(p-(1-bromoethyl)phenyl)boroxine, tris(p-(1-bromoethyl)phenyl)boroxine, tris(p-(dibromomethyl)phenyl) boroxine, tris(m-(trichloromethyl)phenyl)boroxine, tris(o-(1,2-dibromoethyl)phenyl)boroxine, tris(2-(trifluoromethyl) phenyl)boroxine, tris(3-(trifluoromethyl)phenyl)boroxine, tris(4-(trifluoromethyl)phenyl)boroxine, tris(2-(bromomethyl)-6-methylphenyl)boroxine, tris(phenylethyl)boroxine, trichloroboroxine, tribromoboroxine, and so on.

[0041] In the preparation of the optically active oxazaborolidine (II), an amount of the boronic acid (V) is usually from 1 to 5 equivalents, preferably from 1 to 2 equivalents of the optically active β-aminoalcohol (I), or an amount of the boroxine derivative (IV) is usually from 0.3 to 1 equivalent, preferably from 0.3 to 0.8 equivalent of the optically active β-aminoalcohol (I).

[0042] In general, the above reaction is performed in the presence of a solvent. As the solvent, any aprotic solvent may be used. Examples of the solvent are aromatic hydrocarbons such as toluene, benzene, chlorobenzene, etc., aliphatic hydrocarbons such as hexane, heptane, chloroform, dichloroethane, etc., and so on.

[0043] A reaction temperature is usually from 0 to +150°C, preferably from 10 to 120°C, and a reaction time is usually from 10 minutes to 8 hours.

[0044] If desired, the optically active oxazaborolidine (II) may be isolated from the reaction mixture by a per se conventional method such as concentration, distillation, and so on.

[0045] In general, the optically active oxazaborolidine (II) and the metal borohydride are mixed in a solvent which is used in the reduction reaction.

[0046] An amount of the optically active oxazaborolidine (II) is usually from 0.01 to 0.6 mole per one mole of the prochiral ketone, or from 0.05 to 0.9 mole per one mole of the oxime derivative (IV).

[0047] Preferred examples of the metal borohydride are lithium borohydride, sodium borohydride, potassium borohydride, zinc borohydride, and so on. Among them, sodium borohydride is particularly preferred.

[0048] An amount of the metal borohydride is usually at least 0.5 mole, preferably from 0.5 to 1 mole in terms of boron atoms per one mole of the prochiral ketone, or usually from 0.5 to 2.5 moles, preferably from 0.7 to 2 moles in terms of boron atoms per one mole of the oxime derivative (IV).

Preparation of an optically active alcohol through reduction of a prochiral ketone

[0049] The optically active alcohol can be prepared by reacting the prochiral ketone corresponding to the optically active alcohol and the acid with the mixture of the metal borohydride and

i) the borane compound prepared from the optically active β-aminoalcohol (I) and the boron hydride, or from the optically active β-aminoalcohol (I), the metal borohydride and the acid, or
ii) the optically active oxazaborolidine (II).

[0050] A preferred example of the prochiral ketone is a ketone of the formula:

$$R^7\text{-CO-}R^8 \qquad \text{(VII)}$$

wherein R^7 and R^8 are different and represent an alkyl group which may have an substituent, an aryl group which may have a substituent, or an aralkyl group which may have a substituent, or R^7 and R^8 form, together with a carbon atom

of the carbonyl group, a ring or condensed ring optionally having a hetero atom.

[0051] When the reduction reaction is carried out using this prochiral ketone (VII), the corresponding optically active alcohol of the formula (VIII):

$$R^7\text{-}C^*H(OH)\text{-}R^8 \qquad \text{(VIII)}$$

wherein R^7 and R^8 are the same as defined above, and * stands for an asymmetric carbon atom is obtained.

[0052] The alkyl group for R^7 and R^8 has usually 1 to 6 carbon atoms and is optionally substituted with at least one halogen atom, and examples thereof are methyl, ethyl, propyl, butyl, pentyl, cyclopentyl, hexyl, cyclohexyl, chloromethyl, bromomethyl, dichloromethyl, trichloromethyl, difluoromethyl, trifluoromethyl, 2-chloroethyl, 3-chloropropyl, 4-chlorobutyl, and so on.

[0053] Examples of the aryl group for R^7 and R^8 are aromatic hydrocarbon groups having usually 6 to 15 carbon atoms and optionally at least one substituent such as phenyl, 1-naphthyl, 2-naphthyl, etc., and heterocyclic groups such as 2-pyridyl, 3-pyridyl, 4-thiazolyl, etc.

[0054] Examples of the substituent which is optionally present on the aryl group are halogen atoms (e.g. chlorine, bromine, etc.), lower alkyl groups (e.g. methyl, ethyl, propyl, butyl, etc.), lower alkoxy groups (e.g. methoxy, ethoxy, propoxy, etc.), aralkyl groups (e.g. benzyl, etc.), aralkyloxy groups (e.g. benzyloxy, etc.), a cyano group, lower haloalkyl groups having 1 to 6 carbon atoms (e.g. fluoromethyl, trifluoromethyl, chloromethyl, trichloromethyl, etc.).

[0055] Examples of the substituted aryl group are halogen-substituted phenyl (e.g. o-, m- or p-chlorophenyl, o-, m- or p- bromophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, etc.), lower alkyl-substituted phenyl (e.g. o-, m- or p-methylphenyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p- butylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethylphenyl, etc.), lower alkoxy-substituted phenyl (e.g. o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-propoxyphenyl, etc.), benzyloxy-substituted phenyl (e.g. o-, m- or p-benzyloxyphenyl, etc.), cyano-substituted phenyl (e.g. o-, m- or p-cyanophenyl, etc.), 2-trifluoromethyl-4-thiazolyl, 2-methyl-4-thiazolyl, and so on.

[0056] The aralkyl group has usually 7 to 15 carbon atoms and optionally at least one substituent, and examples thereof are benzyl, o-, m- or p-tolylmethyl, o-, m- or p-ethylbenzyl, o-, m- or p-methoxybenzyl, o-, m- or p-ethoxybenzyl, and so on.

[0057] Examples of the ring or condensed ring formed from R^7 and R^8 together with the carbon atom of the carbonyl group are cyclic ketones such as cyclopentenone, cyclohexenone, 1,3-cyclopentanedione, 4-cyclopentene-1,3-dione, etc.; hetero atom- containing cyclic ketones such as 3-oxopyrrolidine, 3-oxopiperidine, 3-oxo-quinuclidine, and N-alkyl or N-aralkyl derivatives of the above cyclic ketones; indaline, tetralinone, and so on.

[0058] Examples of the prochiral ketone (VII) are acetophenone, propiophenone, butyrophenone, 1-acetonaphthone, 2-acetonaphthone, o-methoxyacetophenone, o-ethoxyacetophenone, o-propoxyacetophenone, o-benzyloxyacetophenone, p-tert.-butylacetophenone, 2-acetylpyridine, p-cyanoacetophenone, phenyl benzyl ketone, phenyl o-tolylmethyl ketone, phenyl m-tolylmethyl ketone, phenyl p-tolylmethyl ketone, 2-butanone, 2-pentanone, 2-hexanone, 2-heptanone, 2-octanone, cyclohexyl methyl ketone, cyclohexyl benzyl ketone, 2-chloroacetophenone, 2-bromoacetophenone, 2-bromo-3'-chloroacetophenone, 2-chloro-3'-chloroacetophenone, 2-bromo-3'-bromoacetophenone, 2-bromo-3'-fluoroacetophenone, 2-bromo-3'-methylacetophenone, 2-bromo-3'-ethylacetophenone, 2-bromo-3'-propylacetophenone, 2-bromo-3'-butylacetophenone, 2-bromo-3'-methoxyacetophenone, 2-bromo-3'-ethoxyacetophenone, 2-bromo-3'-propoxyacetophenone, 2-bromo-3'-butoxyacetophenone, 2-bromo-4'-chloroacetophenone, 2-bromo-4'-bromoacetophenone, 2-bromo-4'-fluoroacetophenone, 2-bromo-4'-methylacetophenone, 2-bromo-4'-ethylacetophenone, 2-bromo-4'-propylacetophenone, 2-bromo-4'-butylacetophenone, 2-bromo-4'-methoxyacetophenone, 2-bromo-4'-ethoxyacetophenone, 2-bromo-4'-propoxyacetophenone, 2-bromo-4'-butoxyacetophenone, 2-bromo-2'-chloroacetophenone, 2-bromo-2'-bromoacetophenone, 2-bromo-2'-fluoroacetophenone, 2-bromo-2'-methylacetophenone, 2-bromo-2'-ethylacetophenone, 2-bromo-2'-propylacetophenone, 2-bromo-2'-butylacetophenone, 2-bromo-2'-methoxyacetophenone, 2-bromo-2'-ethoxyacetophenone, 2-bromo-2'-propoxyacetophenone, 2-bromo-2'-butoxyacetophenone, 2-bromo-2'-chloro-3'-methoxyacetophenone, 2-bromo-2'-bromo-3'-methoxyacetophenone, 2-bromo-2'-fluoro-3'-methoxyacetophenone, 2-bromo-3'-methoxy-2'-methyl-acetophenone, 2-bromo-2',3'-dimethoxyacetophenone, 2-bromo-2'-ethoxy-3'-methoxyacetophenone, 2-bromo-2',3'-dichloroacetophenone, 2-bromo-2'-bromo-3'-chloroacetophenone, 2-bromo-3'-chloro-2'-fluoroacetophenone, cyclopentenone, 1,3-cyclopentandione, cyclohexenone, 4-cyclopenten-1,3-dione, 3-oxopyrrolidine, 3-oxopiperidine, 3-oxoquinuclidine, N-alkyl or N-aralkyl derivatives thereof; 2-bromo-3'-chloro-2'-fluoroacetophenone, 2-bromo-3'-chloro-2'-methylacetophenone, 2-bromo-3'-chloro-2'-methoxyacetophenone, 2-bromo-3'-chloro-2'-ethoxyacetophenone, 2-bromo-3'-bromo-4'-chloroacetophenone, 2-bromo-2',4'-dibromoacetophenone, 2-bromo-2'-bromo-4'-fluoroacetophenone, 2-bromo-2'-bromo-4'-methylacetophenone, 2-bromo-2'-bromo-4'-methoxyacetophenone, 2-bromo-4'-chloro-2'-fluoroacetophenone, 2-bromo-2',4'-difluoroacetophenone, 2-bromo-4'-bromo-2'-fluoroacetophenone, 2-bromo-2'-fluoro-4'-methylacetophenone, 2-bromo-2'-fluoro-4'-

methoxyacetophenone, 2-bromo-4'-ethoxy-2'-fluoroacetophenone, 2-bromo-4'-chloro-2'-ethoxyacetophenone, 2-bromo-4'-bromo-2'-ethoxyacetophenone, 2-bromo-4'-fluoro-2'-ethoxyacetophenone, 2-bromo-4'-methyl-2'-ethoxyacetophenone, 2-bromo-4'-methoxy-2'-ethoxyacetophenone, 2-bromo-2',4'-diethoxyacetophenone, 2-bromo-4'-chloro-3'-ethoxyacetophenone, 2-bromo-4'-bromo-3'-ethoxyacetophenone, 2-bromo-4'-fluoro-3'-ethoxyacetophenone, 2-bromo-3'-ethoxy-4'-methylacetophenone, 2-bromo-3'-ethoxy-4'-methoxyacetophenone, 2-bromo-3',4'-diethoxyacetophenone, 2-bromo-5'-bromo-3'-chloroacetophenone, 2-bromo-3',5'-dibromoacetophenone, 2-bromo-5'-bromo-3'-fluoroacetophenone, 2-bromo-5'-bromo-3'-methylacetophenone, 2-bromo-5'-bromo-3'-methoxyacetophenone, 2-bromo-5'-bromo-3'-ethoxyacetophenone, 2-bromo-3'-chloro-5'-ethoxyacetophenone, 2-bromo-3'-bromo-5'-ethoxyacetophenone, 2-bromo-5'-ethoxy-3'-fluoroacetophenone, 2-bromo-5'-ethoxy-3'-methylacetophenone, 2-bromo-5'-ethoxy-3'-methoxyacetophenone, 2-bromo-3',5'-dimethoxyacetophenone, 2-bromo-3',5'-diethoxyacetophenone, 2-bromo-3',5'-dichloroacetophenone, 2-bromo-3',5'-difluoroacetophenone, 2-bromo-2',6'-dichloroacetophenone, 2-bromo-2',4',6'-trichloroacetophenone, 2-bromo-3',4',5'-trichloroacetophenone, 4-bromoacetyl-2-methylthiazole, 4-bromoacetyl-2-trifluoromethylthiazole, and so on.

[0059] Examples of the acid are Brønsted acids such as sulfuric acid, acetic acid, phosphoric acid, methanesulfonic acid, p-toluene-sulfonic acid, hydrogen chloride, etc.; and Lewis acids such as zinc chloride, boron trifluoride, aluminum chloride, aluminum bromide, titanium tetrachloride, tin tetrachloride, tin trichloride, etc.

[0060] An amount of the acid is usually from 0.8 to 1.2 equivalents, preferably from 0.9 to 1.1 equivalents of the metal borohydride in the mixture of the borane compound and the metal borohydride.

[0061] In general, the reduction reaction is performed in the presence of a solvent. Examples of the solvent are ethers (e.g. dioxane; tetrahydrofuran, diglyme, etc.), sulfides (e.g. dimethylsulfide, diethylsulfide, etc.), and mixtures thereof, and mixtures of the above solvent and a hydrocarbon (e.g. benzene, toluene, xylene, chlorobenzene, 1,2-dichloroethane, etc.).

[0062] An amount of the solvent is usually from 1 to 50 wt. parts per one wt. part of the oxime derivative.

[0063] The reduction of the prochiral ketone is carried out by reacting the prochiral ketone and the acid with the mixture of the metal borohydride and the borane compound or the optically active oxazaborolidine (II). Preferably, the prochiral ketone and the acid are dropwise added to the mixture of the metal borohydride and the borane compound or the optically active oxazaborolidine (II). In this case, the prochiral ketone and the acid may be added in admixture or separately. Alternatively, they may be added in the form of a solution in the solvent.

[0064] A reducing temperature is usually 150°C or lower, preferably from -20 to 110°C, more preferably 0 to 100°C.

[0065] A time for dropwise adding the prochiral ketone and the acid is usually from 0.1 to 20 hours. After the dropwise addition of the prochiral ketone and the acid, the reaction mixture is preferably stirred for 0.1 to 10 hours while warming at a temperature in the above range.

[0066] The progress of the reaction can be monitored with an analytical method such as gas chromatography.

[0067] After the reduction reaction, the borane compound or the optically active oxazaborolidine (II) may be decomposed by the addition of an acid such as hydrochloric acid to the reaction mixture, and optionally the solvent is evaporated off. Then, to the reaction mixture, an extraction solvent such as toluene and an aqueous solution of an acid such as hydrochloric acid are added to separate an acid of the optically active β-aminoalcohol (I) with the acid, and the solvent is evaporated off from the separated organic layer to obtain the desired optically active alcohol in the salt form.

[0068] The separated salt of the optically active β-aminoalcohol (I) with the acid is made basic and extracted with an extraction solvent such as toluene, followed by evaporating the solvent off to recover the optically active β-aminoalcohol (I) in the free form.

[0069] The obtained optically active alcohol can be further purified by a per se conventional purification method such as distillation, chromatography, and so on.

Preparation of an optically active amine (III) by reduction of an oxime derivative (IV)

[0070] The optically active amine (III) can be prepared by reacting the oxime derivative (IV) and the acid with the mixture of the metal borohydride and

i) the borane compound prepared from the optically active β-aminoalcohol (I) and the boron hydride, or from the optically active β-aminoalcohol (I), the metal borohydride and the acid, or
ii) the optically active oxazaborolidine (II).

[0071] The oxime derivative (IV) may be an syn-form, an anti-form or a mixture thereof which is rich in one of them.

[0072] In the formula (IV), R^7 and R^8 are different and represent an alkyl group which may have at least one substituent, an aryl group which may have at least one substituent or an aralkyl group which may have at least one substituent, or R^7 and R^8 form, together with the carbon atom of the oxime group, a ring or condensed ring which may

have a hetero atom.

[0073] Examples of the groups for each of R^7 and R^8 are the same as those exemplified in connection with the prochiral ketone (VII).

[0074] Examples of the ring or condensed ring formed from R^7 and R^8 together with the carbon atom of the oxime group are oxime ethers of cyclic ketones (e.g. cyclopentenone, cyclohexenone, etc.), cyclic ketones having a hetero atom (e.g. 3-oxopyrrolidine, 3-oxopiperidine, 3-oxoquinuclidine, N-alkyl or N-aralkyl derivatives thereof, etc.), and benzene-ring condensed cyclic ketones (e.g. indanone, tetralinone, etc.).

[0075] The alkyl group for R^9 has usually 1 to 10 carbon atoms, and examples thereof are methyl, ethyl, propyl, butyl, pentyl, cyclopentyl, hexyl, cyclohexyl, heptyl, cycloheptyl, octyl, nonyl, decyl, etc.

[0076] The aralkyl group for R^9 has usually 7 to 12 carbon atoms, and examples thereof are benzyl, β-phenethyl, naphthylmethyl, etc.

[0077] The alkyl-substituted silyl group has usually 3 to 12 carbon atoms in the alkyl substituents in total, and examples thereof are trimethylsilyl, dimethyl-tert.-butylsilyl, tri-n-propylsilyl, tri-n-butylsilyl, etc.

[0078] Specific examples of the oxime derivative (IV) are O-methyl, O-ethyl, O-octyl, O-cyclohexyl, O-benzyl, and O-trimethylsilyl derivatives of oximes of acetophenone, propiophenone, butyrophenone, 1-acetonaphthone, 2-acetonaphthone, o-, m- or p- methoxyacetophenone, o-ethoxyacetophenone, o-propoxyacetophenone, o-, m- or p-benzyloxyacetophenone, 2-acetylpyridine, p-cyanoacetophenone, phenyl benzyl ketone, phenyl o-tolylmethyl ketone, phenyl m-tolylmethyl ketone, phenyl p-tolylmethyl ketone, 2-butanone, 2-pentanone, 2-hexanone, 2-heptanone, 2-octanone, cyclohexyl methyl ketone, cyclohexyl benzyl ketone, 2-chloroacetophenone, p-tert.-butylacetophenone, p-chloroacetophenone, m-bromoacetophenone, p-bromoacetophenone, p-cyanoacetophenone, 2-chloro-3'-chloroacetophenone, m,p- or o,p-dichloroacetophenone, 3-sulfonamide-4-methoxybenzyl methyl ketone, 3,4-dimethoxybenzyl methyl ketone, 3'-benzyloxyacetophenone, isobutyl 2-piperidinophenyl ketone, cyclopentenone, cyclohexenone, pyrrolidin-2-one, pyrrolidin-3-one, piperidin-2-one, piperidin-3-one, quinuclidin-2-one, quinuclidin-3-one, 2-piperidylmethyl phenyl ketone, 8-methoxytetrahydronaphthalen-2-one, etc.

[0079] They may be the syn- or anti-form, or mixtures thereof in which either one of the syn-form and the anti-form is richer than the other.

[0080] The oxime derivative (IV) may be prepared from the above described prochiral ketone (III) according to a per se conventional method. When one of the syn-form and the anti-form, is used, the rest of them may be transformed to the necessary form by isomerization between the anti-form and the syn-form, whereby the raw material is effectively used.

[0081] Examples of the acid are Brønsted acids such as sulfuric acid, acetic acid, phosphoric acid, methanesulfonic acid, p-toluene-sulfonic acid, hydrogen chloride, etc.; and Lewis acids such as zinc chloride, boron trifluoride, aluminum chloride, aluminum bromide, titanium tetrachloride, tin tetrachloride, tin trichloride, iodine, etc.

[0082] An amount of the acid is usually from 0.8 to 1.2 equivalents, preferably from 0.9 to 1.1 equivalents of the mmetal borohydride.

[0083] In general, the reduction reaction is performed in the presence of a solvent. Examples of the solvent are ethers (e.g. dioxane, tetrahydrofuran, diglyme, etc.), sulfides (e.g. dimethylsulfide, diethylsulfide, etc.), and mixtures thereof, and mixtures of the above solvent and a hydrocarbon (e.g. benzene, toluene, xylene, chlorobenzene, 1,2-dichloroethane, etc.).

[0084] An amount of the solvent is usually from 1 to 50 times the weight of the oxime derivative (III).

[0085] The reduction of the oxime derivative (IV) is carried out by reacting the oxime derivative (IV) and the acid with the mixture of the metal borohydride and the borane compound or the optically active oxazaborolidine (II). Preferably, the oxime derivative (IV) and the acid is added to the mixture of the metal borohydride and the borane compound or the optically active oxazaborolidine (II). In this case, they may be added in admixture or separately, or in the form of a solution in the solvent.

[0086] The reduction reaction can be accelerated by the use of a transition metal halide (e.g. cobalt chloride, nickel chloride, cesium chloride, etc.) in an amount of 0.1 to 5 mole % based on the oxime derivative (IV).

[0087] A reaction temperature is usually 150°C or lower, preferably from -20 to +110°C, more preferably from 0 to 100°C.

[0088] A time for adding the oxime derivative and the acid is usually from 0.1 to 10 hours. After the addition of the oxime derivative and the acid, the reaction mixture is preferably stirred for 1 to 30 hours while warming at a temperature in the above range.

[0089] The progress of the reaction can be monitored with an analytical method such as gas chromatography.

[0090] After the reduction reaction, the borane compound or the optically active oxazaborolidine (II) may be decomposed by the addition of an acid such as hydrochloric acid to the reaction mixture, to obtain the optically active β-aminoalcohol (I) and the optically active amine (III), which are separated by utilizing a difference of their solubilities in a solvent, or distillation.

[0091] The obtained optically active amine (I) can be further purified by a per se conventional purification method

such as recrystallization in the form of a salt with the acid, distillation, chromatography, and so on.

[0092] The optically active β-aminoalcohol separated can be recovered in the same manner as in the above chapter of "Preparation of optically active alcohol".

[0093] According to the present invention, the optically active alcohol having a high optical purity can be prepared by using the metal borohydride which is cheap and available in an industrial scale as a hydrogen source.

[0094] In addition, the amount of the used metal borohydride or boron hydride is decreased and the optically active alcohol is effectively prepared.

[0095] Further, the optically active amine is prepared effectively with decreasing the used amount of the metal borohydride or boron hydride as the hydrogen source.

EXAMPLES

[0096] The present invention will be illustrated by the following Examples, which will not limit the scope of the present invention in any way.

Example 1

[0097] Under a nitrogen atmosphere, sodium borohydride (0.38 g, 10 mmol) was suspended in a solution of (1S, 2R)-(+)-norephedrine (0.151 g, 1 mmol) in dioxane (10 ml). To the suspension, a mixture of 96 % sulfuric acid (0.102 g, 1 mmol) and dioxane (1 ml) was added, followed by stirring at 65 to 70°C for 30 minutes to obtain a mixture of a borane compound and sodium borohydride.

[0098] To this mixture, a mixture of 96 % sulfuric acid (0.408 g, 4 mmol), acetophenone (2.16 g, 18 mmol) and dioxane (20 ml) was dropwise added over 100 minutes at the same temperature, and then stirred for 30 minutes.

[0099] After cooling to room temperature, the 10 % hydrochloric acid (20 ml) was added, and then the mixture was extracted with toluene (each 20 ml) twice. The organic layer was washed with water (each 20 ml) twice, and analyzed by gas chromatography to find that the conversion was 100 %. The washed extract was also analyzed by high performance liquid chromatography (HPLC) using an optically active column to find that obtained optically active α-phenethyl alcohol consisted of 10.4 % of the (R)- isomer and 89.6 % of the (S)-isomer.

Example 2

[0100] In the same manner as in Example 1 except that a mixture of 96 % sulfuric acid (0.408 g, 4 mmol), acetophenone (2.16 g, 18 mmol) and dioxane (10 ml) was dropwise added while refluxing dioxane (101°C), the reactions were performed.

[0101] The conversion was 100 %, and the obtained optically active α-phenethyl alcohol consisted of 12.2 % of the (R)- isomer and 87.8 % of the (S)-isomer.

Example 3

[0102] In the same manner as in Example 1 except that tetrahydrofuran was used in place of dioxane, and the mixture was stirred for 30 minutes while refluxing tetrahydrofuran (65°C) instead of the stirring at 65-70°C for 30 minutes, a mixture of the borane compound and sodium borohydride was prepared.

[0103] Then, in the same manner as in Example 1 except that a mixture of 96 % sulfuric acid (0.408 g, 4 mmol), acetophenone (1.2 g, 10 mmol) and tetrahydrofuran (6 ml) was dropwise added over 60 minutes at the same temperature, and thereafter a mixture of acetophenone (1.2 g, 10 mmol) and tetrahydrofuran (6 ml) was dropwise added over 60 minutes, the reaction was performed.

[0104] The conversion was 92 %, and the obtained optically active α-phenethyl alcohol consisted of 14.3 % of the (R)- isomer and 85.7 % of the (S)-isomer.

Example 4

[0105] In the same manner as in Example 1 except that (1R,2S)-2-amino-1,2-diphenylethanol (0.213 g, 1 mmol) was used in place of (1S,2R)-(+)-norephedrine, the reactions were performed.

[0106] The conversion was 100 %, and the obtained optically active α-phenethyl alcohol consisted of 6.4 % of the (R)- isomer and 93.6 % of the (S)-isomer.

Example 5

[0107] In the same manner as in Example 1 except that (S)-α,α-diphenyl-2-pyrrolidinemethanol (0.253 g, 1 mmol) was used in place of (1S,2R)-(+)-norephedrine, the reactions were performed.

[0108] The conversion was 100 %, and the obtained optically active α-phenethyl alcohol consisted of 3.2 % of the (R)- isomer and 96.8 % of the (S)-isomer.

Example 6

[0109] Under a nitrogen atmosphere, sodium borohydride (0.378 g, 10 mmol) was suspended in a solution of (1S, 2R)-(+)-norephedrine (0.1512 g, 1 mmol) in dioxane (10 ml). To the suspension, a mixture of 100 % sulfuric acid (0.098 g, 1 mmol) and dioxane (1 ml) was added over 10 minutes, followed by stirring at 75 to 80°C for 1 hour to obtain a mixture of a borane compound and sodium borohydride.

[0110] To this mixture, a mixture of 100% sulfuric acid (0.392 g, 4 mmol), phenacyl chloride (1.546 g, 10 mmol) and dioxane (5 ml) was dropwise added over 15 minutes at the same temperature, and then stirred for 30 minutes at the same temperature.

[0111] After cooling to room temperature, the 10 % hydrochloric acid (10 ml) was added, and then the mixture was extracted with toluene (each 20 ml) twice. The organic layer was washed with water (each 30 ml) twice to obtain a solution of optically active 2-chloro-1-phenylethanol in toluene.

[0112] The conversion was 100 %, and the obtained optically active 2-chloro-1-phenylethanol consisted of 87.3 % of the (R)-isomer and 12.7 % of the (S)-isomer.

Example 7

[0113] In the same manner as in Example 6 except that (1S,2R)-2-amino-1-(2,5-dimethoxyphenyl)-1-propanol (1 mmol) was used in place of (1S,2R)-(+)-norephedrine, the reactions were performed.

[0114] The conversion was 100 %, and the obtained optically active 2-chloro-1-phenylethanol consisted of 84.6 % of the (R)-isomer and 15.4 % of the (S)-isomer.

Example 8

[0115] In the same manner as in Example 6 except that (1S,2R)-2-amino-1-(2,5-dimethylphenyl)-1-propanol (1 mmol) was used in place of (1S,2R)-(+)-norephedrine, the reactions were performed.

[0116] The conversion was 100 %, and the obtained optically active 2-chloro-1-phenylethanol consisted of 82.7 % of the (R)-isomer and 17.3 % of the (S)-isomer.

Example 9

[0117] In the same manner as in Example 6 except that (1S,2R)-1,2-diphenyl-2-aminoethanol (1 mmol) was used in place of (1S,2R)-(+)-norephedrine, the reactions were performed.

[0118] The conversion was 100 %, and the obtained optically active 2-chloro-1-phenylethanol consisted of 84.5 % of the (R)-isomer and 15.5 % of the (S)-isomer.

Example 10

[0119] In the same manner as in Example 6 except that propiophenone was used in place of phenacyl chloride, 98 % sulfuric acid was used in place of 100 % sulfuric acid, and the mixture of the 98 % sulfuric acid (4 mmol), propiophenone (10 mmol) and dioxane (5 ml) was dropwise added over 30 minutes, the reactions were performed.

[0120] The conversion was 100 %, and the obtained optically active 2-chloro-1-phenylpropanol consisted of 19 % of the (R)-isomer and 81 % of the (S)-isomer.

Example 11

[0121] Under a nitrogen atmosphere, a solution of 1M boranetetrahydrofuran complex (2 ml, 2 mmol) in tetrahydrofuran was added to a solution of (1S,2R)-(+)-norephedrine (0.1512 g, 1 mmol) in dioxane (8 ml) at 10 to 12°C, followed by stirring at 75 to 80°C for 1 hour to obtain a borane compound.

[0122] In the borane compound solution, sodium borohydride (0.303 g, 8 mmol) was suspended at 45 to 50°C, and then, to the suspension, a mixture of 98 % sulfuric acid (0.4 g, 4 mmol), propiophenone (1.342 g, 10 mmol) and dioxane

(5 ml) was added over 35 minutes, followed by stirring at the same temperature for 30 minutes. Thereafter, the reaction mixture was post-treated in the same manner as in Example 6.

[0123] The conversion was 99.9 %, and the obtained optically active 1-phenylpropanol consisted of 18.3 % of the (R)-isomer and 81.7 % of the (S)-isomer.

Example 12

[0124] Under a nitrogen atmosphere, sodium borohydride (0.0908 g, 2.4 mmol) was suspended in a solution of (R)-(-)-phenylglycinol (0.0274 g, 0.2 mmol) in tetrahydrofuran (10 ml). To the suspension, a solution of iodine (0.203 g, 0.8 mmol) in tetrahydrofuran (1 ml) was added over about 10 minutes, followed by stirring at 65°C for 1.75 hours to obtain a mixture of a borane compound and sodium borohydride.

[0125] To this mixture, a mixture of iodine (0.203 g, 0.8 mmol), acetophenone (0.24 g, 2 mmol) and tetrahydrofuran (1 ml) was dropwise added over 25 minutes, and stirred for 30 minutes at the same temperature.

[0126] After cooling to room temperature, the 10 % hydrochloric acid (10 ml) was added, and then the mixture was extracted with toluene (each 20 ml) twice. The organic layer was washed with water (each 20 ml) twice to obtain a solution of optically active α-phenethyl alcohol in toluene.

[0127] The conversion was above 99.9 %, and the obtained optically active α-phenethyl alcohol consisted of 94.4 % of the (R)-isomer and 5.6 % of the (S)-isomer.

Example 13

[0128] In the same manner as in Example 13 except that (1S,2R)-(+)-norephedrine (0.2 mmol) was used in place of (R)-(-)-phenylglycinol, the reactions were performed.

[0129] The conversion was above 99.9 %, and the obtained optically active α-phenethyl alcohol consisted of 89.4 % of the (R)-isomer and 10.6 % of the (S)-isomer.

Comparative Example 1

[0130] In the same manner as in Example 10 except that a mixture of 98 % sulfuric acid (4 mmol) and dioxane (4 ml) was dropwise added over 10 minutes in place of dropwise addition of the mixture of 98 % sulfuric acid (4 mmol), propiophenone (10 mmol) and dioxane (5 ml) over 30 minutes, and the mixture of propiophenone (10 mmol) and dioxane (2 ml) was dropwise added over 10 minutes, and thereafter the mixture was stirred for 1.5 hours, the reactions were performed.

[0131] The conversion was 2.7 %, and the obtained optically active 1-phenylpropanol consisted of 40.4 % of the (R)-isomer and 59.6 % of the (S)-isomer.

Example 14

[0132] Under a nitrogen atmosphere, sodium borohydride (0.167 g, 4.4 mmol) was suspended in a solution of (R)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (0.1224 g, 0.44 mmol) in dioxane (5 ml) (manufactured by Aldrich). To the suspension, a mixture of 98 % sulfuric acid (0.221 g, 2.2 mmol), propiophenone (0.651 g, 4.9 mmol) and dioxane (2.5 ml) was added over 30 minutes at 75 to 80°C, followed by stirring at the same temperature for 30 minutes.

[0133] After the above reaction, the 10 % hydrochloric acid (8 ml) was added, and then the mixture was extracted with toluene (each 15 ml) twice. The organic layer was washed with water (each 20 ml) twice, and analyzed by gas chromatography to find that the conversion was 99.9 %. The washed organic layer was also analyzed by high performance liquid chromatography (HPLC) using an optically active column to find that obtained optically active 1-phenyl-1-propanol consisted of 11.3 % of the (R)- isomer and 88.7 % of the (S)-isomer.

Comparative Example 2

[0134] In the same manner as in Example 14 except that the mixture of 98 % sulfuric acid (2.2 mmol) and dioxane (1.5 ml) was dropwise added over 20 minutes instead of the dropwise addition of the mixture of 98 % sulfuric acid (2.2 mmol), propiophenone (4.9 mmol) and dioxane (2.5 ml) over 30 minutes, and then the solution of propiophenone (4.9 mmol) in dioxane (1.5 ml) was dropwise added over 10 minutes, the reactions were performed.

[0135] The conversion was 2.6 %, and the obtained optically active 1-phenylpropanol consisted of 48.2 % of the (R)-isomer and 51. 8 % of the (S)-isomer.

Example 15

[0136] Under a nitrogen atmosphere, sodium borohydride (0.38 g, 10 mmol) was suspended in a solution of (1S, 2R)-norephedrine (0.68 g, 4.5 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio = 1:1) (10 ml) at room temperature. To the suspension, a solution of 100 % sulfuric acid (0.245 g, 2.5 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio = 1:1) (2.5 ml) was added over 20 minutes at room temperature, followed by stirring at 70 to 75°C for 1 hour to obtain a mixture of a borane compound and sodium borohydride.

[0137] To this mixture, a solution of 100 % sulfuric acid (0.245 g, 2.5 mmol) and anti-2',4'-dichloroacetophenone(O-methyl)oxime (1.09 g, 5 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio = 1:1) (2.5 ml) was dropwise added over 30 minutes at 45 to 50°C, and stirred for 14 hours at the same temperature and then for 8 hours at 75 to 80°C.

[0138] After cooling to room temperature, the 10 % hydrochloric acid (10 ml) was added, and then the mixture was made alkaline by the addition of a 20 % aqueous solution of sodium hydroxide. Then, the mixture was extracted with toluene (each 15 ml) twice, and the organic layer was washed with water (each 15 ml) twice to obtain a solution of optically active α-2',4'-dichlorophenylethylamine in toluene.

[0139] The conversion was 96.7 %, and the obtained product contained 85.5 % of α-2',4'-dichlorophenylethylamine and 14.5 % of N-methoxy-α-2',4'-dichlorophenylethylamine. The optically active α-2',4'-dichlorophenylethylamine consisted of 93 % of the (R)-isomer and 7 % of the (S)-isomer.

Example 16

[0140] Under a nitrogen atmosphere, sodium borohydride (1.665 g, 0.044 mol) was suspended in a solution of (1S, 2R)-norephedrine (6.05 g, 0.04 mol) in tetrahydrofuran (50 ml), and cooled to 10°C. To the suspension, a solution of 100 % sulfuric acid (2.157 g, 0.022 mol) in tetrahydrofuran (50 ml) was added over 40 minutes at 10 to 15°C. Toluene (50 ml) was added and then the mixture was stirred at 70 to 75°C for 1 hour to obtain a borane compound.

[0141] To this mixture which was cooled to 45°C, sodium borohydride (2.118 g, 0.056 g) was added and then a solution of 100 % sulfuric acid (2.754 g, 0.028 ml) and anti-2',4'-dichloroacetophenone(O-methyl)oxime (10.9 g, 0.05 mol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio = 1:1) (30 ml) was dropwise added over 40 minutes at 45 to 50°C, and stirred for 3 hours at the same temperature and then for 8 hours at 75 to 80°C. Thereafter, cobalt chloride (0.0325 g) was added, and the mixture was further stirred for 3 hours at the same temperature.

[0142] After cooling to room temperature, the 10 % hydrochloric acid (40 ml) was added, and then the mixture was made alkaline by the addition of a 20 % aqueous solution of sodium hydroxide. Then, the mixture was extracted with toluene (each 40 ml) twice, and the organic layer was washed with water (each 40 ml) twice to obtain a solution of optically active α-2',4'-dichlorophenylethylamine in toluene.

[0143] The conversion was 98.3 %, and the obtained product contained 99.8 % of α-2',4'-dichlorophenylethylamine and 0.2 % of N-methoxy-α-2',4'-dichlorophenylethylamine. The optically active α-2',4'-dichlorophenylethylamine consisted of 90.7 % of the (R)-isomer and 9.3 % of the (S)-isomer.

Example 17

[0144] In the same manner as in Example 15 except that (1S,2R)-2-amino-1,2-diphenylethanol (0.96 g, 4.5 mmol) was used in place of (1S,2R)-norephedrine, the reactions were performed.

[0145] The conversion was above 99.9 %, and the obtained product contained 96.4 % of the amine compound and 3.6 % of the N-methoxy derivative. The optically active compound consisted of 85.4 % of the (R)-isomer and 14.6 % of the (S)-isomer.

Example 18

[0146] In the same manner as in Example 15 except that (1S,2R)-2-amino-1-(2,5-dimethoxyphenyl)propanol (0.89 g, 4.5 mmol) was used in place of (1S,2R)-norephedrine, the reactions were performed.

[0147] The conversion was 97.2 %, and the obtained product contained 96.6 % of the amine compound and 3.4 % of the N-methoxy derivative. The optically active compound consisted of 86.5 % of the (R)-isomer and 13.5 % of the (S)-isomer.

Example 19

[0148] In the same manner as in Example 15 except that (1S,2R)-2-amino-1-(2,5-dimethylphenyl)propanol (0.81 g, 4.5 mmol) was used in place of (1S,2R)(1S,2R)-norephedrine, the reactions were performed.

[0149] The conversion was 96.3 %, and the obtained product contained 96.8 % of the amine compound and 3.2 % of the N-methoxy derivative. The optically active compound consisted of 81.9 % of the (R)-isomer and 18.1 % of the (S)-isomer.

Example 20

[0150] Under a nitrogen atmosphere, a solution of 1M boranetetrahydrofuran complex (4.5 ml, 4.5 mmol) was added to a solution of (1S,2R)-norephedrine (0.605 g, 4 mmol) in tetrahydrofuran (0.510 ml) and toluene (5 ml) at 10 to 15°C, followed by stirring at 75 to 80°C for 1 hour to obtain a borane compound.

[0151] After cooling to room temperature, sodium borohydride (0.208 g, 5.5 mol) was added, and then a solution of 100 % sulfuric acid (0.27 g, 2.75 mmol) and anti-2',4'-dichloroacetophenone(O-methyl)oxime (1.09 g, 5 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio = 1:1) (5 ml) was dropwise added over 30 minutes at 45 to 50°C, followed by stirring at the same temperature for 14.5 hours, and then at 75 to 80°C for 10 hours.

[0152] Thereafter, the reaction mixture was post-treated and analyzed in the same manner as in Example 15.

[0153] The conversion was 83.7 %, and the obtained product contained 81.3 % of the amine compound and 18.7 % of the N-methoxy derivative. The optically active compound consisted of 92.8 % of the (R)-isomer and 7.2 % of the (S)-isomer.

Example 21

[0154] Under a nitrogen atmosphere, sodium borohydride (0.076 g, 2 mmol) was suspended in a solution of (1S, 2R)-norephedrine (0.121 g, 0.8 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio = 1:1) (2 ml). To the suspension, a solution of 98 % sulfuric acid (0.045 g, 0.45 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio = 1:1) (0.45 ml) was added over 10 minutes at 15 to 20°C, followed by stirring at 75 to 80°C for 1 hour to obtain a mixture of a borane compound and sodium borohydride.

[0155] To this mixture, a solution of 98 % sulfuric acid (0.055 g, 0.55 mmol) and p-tolylmethyl phenyl ketone(O-methyl)oxime (a ratio of anti-form to syn-form = 93.5:6.5) (0.239 g, 1 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio = 1:1) (0.55 ml) was dropwise added over 20 minutes at 45 to 50°C, and stirred for 19.5 hours at the same temperature and then for 10 hours at 75 to 80°C.

[0156] Thereafter, the reaction mixture was post-treated and analyzed in the same manner as in Example 15.

[0157] The conversion was 90.8 %, and the obtained product contained 95.6 % of 2-(p-tolyl)-1-phenylethylamine and 4.4 % of N-methoxy-2-(p-tolyl)-1-phenylethylamine. The optically active 2-(p-tolyl)-1-phenylethylamine consisted of 88.9 % of the (R)-isomer and 11.1 % of the (S)-isomer.

Example 22

[0158] Under a nitrogen atmosphere, sodium borohydride (0.32 g, 8.5 mmol) was suspended in a solution of (R)-2-amino-1,1,3-triphenyl-1-propanol (0.68 g, 2.0 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio = 1:1) (10 ml). To the suspension which was cooled to 10°C, a solution of 100 % sulfuric acid (0.07 g, 0.75 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio = 1:1) (1 ml) was added over 30 minutes at 10 to 15°C, followed by stirring at 45 to 50°C for 1 hour to obtain a mixture of a borane compound and sodium borohydride.

[0159] To this mixture, a solution of 100 % sulfuric acid (0.34 g, 3.5 mmol) and anti-2',4'-dichloroacetophenone(O-methyl)oxime (1.09 g, 5 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio = 1:1) (2.0 ml) was dropwise added over 30 minutes at 45 to 50°C, and stirred for 5 hours at the same temperature and then for 14 hours at 75 to 80°C.

[0160] After cooling to room temperature, the 10 % hydrochloric acid (10 ml) was added, and then the mixture was made alkaline by the addition of a 20 % aqueous solution of sodium hydroxide. Then, the mixture was extracted with toluene (each 15 ml) twice, and the organic layer was washed with water (each 15 ml) twice.

[0161] The conversion was 100 %, and the product contained 99.9 % of α-2',4'-dichlorophenylethylamine and 0.1 % of N-methoxy-α-2',4'-dichlorophenylethylamine.

[0162] The optically active α-2',4'-dichlorophenylethylamine consisted of 97.1 % of the (R)-isomer and 2.9 % of the (S)-isomer.

Example 23

[0163] In the same manner as in Example 22 except that (S)-2-amino-3-methyl-1,1-diphenyl-1-butanol (0.38 g, 1.5 mmol) was used in place of (R)-2-amino-1,1,3-triphenyl-1-propanol, the reactions were performed.

[0164] The conversion was 97.9 %, and the obtained product contained 93.7 % of the amine compound and 6.3 %

of the N-methoxy derivative. The optically active compound consisted of 97.0 % of the (S)-isomer and 3.0 % of the (R)-isomer.

Example 24

[0165] In the same manner as in Example 22 except that (S)-2-amino-4-methyl-1-pentanol (0.17 g, 1.5 mmol) was used in place of (R)-2-amino-1,1,3-triphenyl-1-propanol, the reactions were performed.

[0166] The conversion was 97.2 %, and the obtained product contained 93.1 % of the amine compound and 6.9 % of the N-methoxy derivative. The optically active compound consisted of 90.5 % of the (S)-isomer and 9.5 % of the (R)-isomer.

Example 25

[0167] In the same manner as in Example 22 except that (S)-2-amino-3-methyl-1-butanol (0.16 g, 1.5 mmol) was used in place of (R)-2-amino-1,1,3-triphenyl-1-propanol, the reactions were performed.

[0168] The conversion was 97.6 %, and the obtained product contained 86.2 % of the amine compound and 13.8 % of the N-methoxy derivative. The optically active compound consisted of 89.4 % of the (S)-isomer and 10.6 % of the (R)-isomer.

Example 26

[0169] Under a nitrogen atmosphere, sodium borohydride (0.32 g, 8.5 mmol) was suspended in a solution of (R)-2-amino-1,1-diphenyl-1-propanol (0.45 g, 2.0 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio = 1:1) (10 ml). To the suspension which was cooled to 10°C, a solution of 100 % sulfuric acid (0.07 g, 0.75 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio = 1:1) (1 ml) was added over 30 minutes at 10 to 15°C, followed by stirring at 45 to 50°C for 1 hour to obtain a mixture of a borane compound and sodium borohydride.

[0170] To this mixture, a solution of 100 % sulfuric acid (0.34 g, 3.5 mmol) and anti-2',4'-dichloroacetophenone(O-methyl)oxime (1.09 g, 5 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio = 1:1) (2.0 ml) was dropwise added over 30 minutes at 45 to 50°C, and stirred for 5 hours at the same temperature and then for 14 hours at 75 to 80°C.

[0171] After cooling to room temperature, the 10 % hydrochloric acid (10 ml) was added, and then the mixture was made alkaline by the addition of a 20 % aqueous solution of sodium hydroxide. Then, the mixture was extracted with toluene (each 15 ml) twice, and the organic layer was washed with water (each 15 ml) twice.

[0172] The conversion was 100 %, and the product contained 99.9 % of the amine compound and 0.1 % of the N-methoxy derivative.

[0173] The optically active amine compound consisted of 97.1 % of the (R)-isomer and 2.9 % of the (S)-isomer.

Example 27

[0174] Under a nitrogen atmosphere, sodium borohydride (0.378 g, 10.0 mmol) was suspended in a solution of (R)-2-amino-1,1-diphenyl-1-propanol (0.909 g, 4.0 mmol) in tetrahydrofuran (10 ml). To the suspension which was cooled to 10°C, a solution of 100 % sulfuric acid (0.22 g, 2.25 mmol) in tetrahydrofuran (1 ml) was added over 30 minutes at 10 to 15°C, followed by stirring at 45 to 50°C for 1 hour to obtain a mixture of a borane compound and sodium borohydride.

[0175] To this mixture, toluene (5 ml) was dropwise added over 30 minutes at the same temperature, and then a solution of 100 % sulfuric acid (0.27 g, 2.75 mmol) and 3'-methoxyacetophenone(O-methyl)oxime (a ratio of anti-form to syn-form = 98.4:1.6) (0.896 g, 5 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio = 2:1) (3.0 ml) was dropwise added over 45 minutes, and stirred for 19.5 hours at the same temperature and then for 7.5 hours at 75 to 80°C.

[0176] After cooling to room temperature, the 10 % hydrochloric acid (10 ml) was added, and then the mixture was made alkaline by the addition of a 23 % aqueous solution of sodium hydroxide. Then, the mixture was extracted with n-hexane (each 15 ml) twice, and the organic layer was washed with water (each 15 ml) twice.

[0177] The conversion was 99.9 %, and the product contained 99.9 % of α-3'-methoxyphenylethylamine and 0.1 % of N-methoxy-α-3'-methoxyphenylethylamine.

[0178] The optically active α-3'-methoxyphenylethylamine consisted of 95.9 % of the (R)-isomer and 4.1 % of the (S)-isomer.

Example 28

[0179] In the same manner as in Example 27 except that (1S,2R)-2-amino-1-phenyl-1-propanol (0.605 g, 4.0 mmol) was used in place of (R)-2-amino-1,1-diphenyl-1-propanol, the reactions were performed.

[0180] The conversion was 99.3 %, and the obtained product contained 89.0 % of the amine compound and 11.0 % of the N-methoxy derivative. The optically active compound consisted of 92.7 % of the (R)-isomer and 7.3 % of the (S)-isomer.

Example 29

[0181] In the same manner as in Example 27 except that (R)-2-amino-2-phenylethanol (0.605 g, 4.0 mmol) was used in place of (R)-2-amino-1,1-diphenyl-1-propanol, the reactions were performed.

[0182] The conversion was 95.3 %, and the obtained product contained 98.6 % of the amine compound and 1.4 % of the N-methoxy derivative. The optically active compound consisted of 89.1 % of the (R)-isomer and 10.9 % of the (S)-isomer.

Example 30

[0183] Under a nitrogen atmosphere, sodium borohydride (0.121 g, 3.2 mmol) was suspended in a solution of (R)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (0.333 g, 1.2 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio of 1:1) (5 ml) (manufactured by Aldrich). To the suspension, a solution of 98 % sulfuric acid (0.16 g, 1.6 mmol) and anti-phenyl p-tolyl ketone(O-methyl)oxime (ratio of anti-form to syn-form = 93.5:6.5) (0.383 g, 1.6 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio of 1:1) (3 ml) was added over 30 minutes at 45 to 50°C, followed by stirring at the same temperature for 4 hours, and then at 75 to 80°C for 24 hours.

[0184] After the above reaction, the 10 % hydrochloric acid (8 ml) was added, and then the mixture was extracted with toluene (each 10 ml) twice. The organic layer was washed with water (each 15 ml) twice to obtain a solution of (R)-1-phenyl-2-(p-tolyl)ethylamine in toluene.

[0185] The product was analyzed by gas chromatography to find that the conversion was 69.8 % and the selectivity was 90.1 %. The product was also analyzed by high performance liquid chromatography (HPLC) using an optically active column to find that obtained the optical purity was 51 %(R).

Comparative Example 1

[0186] In the same manner as in Example 30 except that a solution of 98 % sulfuric acid (1.6 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio of 1:1) (3 ml) was dropwise added over 30 minutes instead of the dropwise addition of the solution of 98 % sulfuric acid (1.6 mmol) and anti-phenyl p-tolyl ketone(O-methyl)oxime (1.6 mmol) in a mixed solvent of toluene and tetrahydrofuran (volume ratio of 1:1) (1 ml), the reactions were performed.

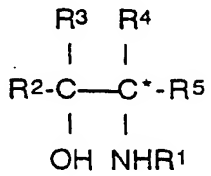
[0187] The conversion was 50.9 %, the selectivity was 76.5 %, and the optical purity was 47.4 %(R).

Claims

1. A process for preparing an optically active alcohol comprising reacting a prochiral ketone corresponding to the optically active alcohol and an acid with a mixture which comprises

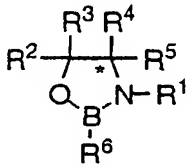
   (1) a boron-containing compound selected from the group consisting of

   i) a borane compound which is obtained from an optically active β-aminoalcohol of the formula (I):



(I)

wherein R^1 is a hydrogen atom, a lower alkyl group or an aralkyl group which may have at least one substituent, R^2, R^3, R^4 and R^5 represent independently each other a hydrogen atom, a lower alkyl group, an aryl group which may have at least one substituent, or an aralkyl group which may have a substituent, provided that R^4 and R^5 are different, that R^1 and R^5 may together form a lower alkylene group, or that R^3 and R^4 may together form a lower alkylene group which may have optionally a substituent or with which a benzene ring is condensed, and * stands for an asymmetric carbon atom, and a boron hydride; or obtained from said optically active β-aminoalcohol (I), a metal borohydride and an acid wherein the amount of the optically active β-aminoalcohol (I) is from 0.005 to 0.5 mole per one mole of the prochiral ketone, and ii) an optically active oxazaborolidine of the formula (II):



(II)

wherein R^1, R^2, R^3, R^4, R^5 and * are the same as defined above, and R^6 is a hydrogen atom, a halogen atom, an alkyl group which may be substituted by at least one halogen atom, an aryl group which may have at least one substituent or an aralkyl group which may have at least one substituent,

and

(2) a metal borohydride.

2. The process according to claim 1, wherein a mixture of said prochiral ketone and said acid is reacted with said mixture of the borane compound and the metal borohydride.

3. The process according to claim 1, wherein said prochiral ketone and said acid are added to said mixture of the borane compound and the metal borohydride separately.

4. The process according to any of claims 1 to 3, wherein an amount of said optically active β-aminoalcohol (I) in the mixture of the borane compound and the metal borohydride is from 0.01 to 0.5 mole per one mole of said prochiral ketone.

5. The process according to any of claims 1 to 4, wherein an amount of said metal borohydride in the mixture of the borane compound and the metal borohydride is from 0.3 to 3 moles per one mole of said prochiral ketone.

6. The process according to any of claims 1 to 5, wherein said prochiral ketone is a ketone of the formula:

$$R^7\text{-CO-}R^8 \qquad \text{(VII)}$$

wherein R^7 and R^8 are different and represent an alkyl group which may have an substituent, an aryl group which may have a substituent, or an aralkyl group which may have a substituent, or R^7 and R^8 form, together with a carbon atom of the carbonyl group, a ring or condensed ring having optionally a hetero atom, and the optically active alcohol prepared is an optically active alcohol of the formula (VIII):

$$R^7\text{-C*H(OH)-}R^8 \qquad \text{(VIII)}$$

wherein R^7 and R^8 are the same as defined above, and * stands for an asymmetric carbon atom

7. The process according to claim 6, wherein R^7 and R^8 are groups selected from the group consisting of an alkyl group which may have an substituent and an aryl group which may have a substituent.

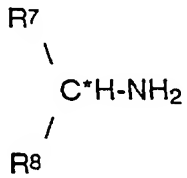
8. The process according to claim 7, wherein R^7 and R^8 are groups selected from the group consisting of alkyl groups, halogenated alkyl groups, aryl groups, haloaryl groups, alkoxyalkyl-substituted aryl groups and aralkyloxy-substituted aryl groups.

9. The process according to any of claims 1 to 8, wherein said acid to be used together with said prochiral ketone is at least one acid selected from the group consisting of Brønsted acids and Lewis acids.

10. The process according to claim 1, wherein a mixture of said prochiral ketone and said acid is reacted with said mixture of the optically active oxazaborolidine and the metal borohydride.

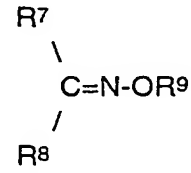
11. The process according to claim 1, wherein said prochiral ketone and said acid are added to said mixture of the optically active oxazaborolidine and the metal borohydride separately.

12. A process for preparing an optically active amine of the formula (III):



(III)

wherein R^7 and R^8 are different and represent an alkyl group which may have at least one substituent, an aryl group which may have at least one substituent or an aralkyl group which may have at least one substituent, or R^7 and R^8 form, together with the carbon atom bonded to the amino group, a ring or condensed ring which may have a hetero atom, and * is the same as defined above comprising reacting an oxime derivative of the formula (IV):



(IV)

wherein R^7 and R^8 are the same as defined above, and R^9 is an alkyl group, an aralkyl group or an alkyl-substituted silyl group and an acid with a mixture which comprises

(1) a boron-containing compound selected from the group consisting of

i) a borane compound which is obtained from an optically active β-aminoalcohol of the formula (I) as defined in claim 1 and a boron hydride, or obtained from said optically active β-aminoalcohol (I), a metal borohydride and an acid wherein the amount of the optically active β-aminoalcohol (I) is from 0.01 to 0.9 mole per one mole of the oxime derivative (IV), and

ii) an optically active oxazaborolidine of the formula (II) as defined in claim 1 and (2) a metal borohydride.

13. The process according to claim 12, wherein said oxime derivative (IV) is a syn-form, an anti-form or a mixture thereof which is rich in one of them.

14. The process according to claim 12, wherein a mixure of said oxime derivative and said acid is reacted with said mixture of the borane compound and the metal borohydride.

15. The process according to claim 12, wherein said oxime derivative and said acid are added to said mixture of the borane compound and the metal borohydride separately.

16. The process according to claim 12, wherein a mixture of said oxime derivative and said acid is reacted with said mixture of the optically active oxazaborolidine and the metal borohydride.

17. The process according to claim 12, wherein said oxime derivative and said acid are added to said mixture of the optically active oxazaborolidine and the metal borohydride separately.

18. The process according to any of claims 12 to 17, wherein R^7 and R^8 are groups selected from the group consisting of an alkyl group which may have an substituent and an aryl group which may have a substituent.

19. The process according to claim 18, wherein R^7 and R^8 are groups selected from the group consisting of alkyl groups, halogenated alkyl groups, aryl groups, haloaryl groups, alkoxyalkyl-substituted aryl groups and aralkyloxy-substituted aryl groups.

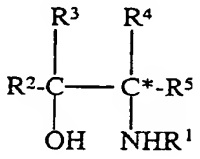
20. The process according to any of claims 12 to 19, wherein said acid to be used together with said oxime derivative (IV) is at least one acid selected from the group consisting of Brønsted acids and Lewis acids.

Patentansprüche

1. Verfahren zur Herstellung eines optisch aktiven Alkohols, umfassend das Umsetzen eines prochiralen Ketons, entsprechend dem optisch aktiven Alkohol, und einer Säure mit einem Gemisch, umfassend:

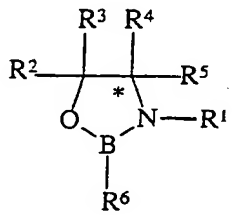
(1) eine borhaltige Verbindung, ausgewählt aus der Gruppe bestehend aus

i) einer Boranverbindung, die aus einem optisch aktiven β-Aminoalkohol der Formel (I):



(I)

in der R^1 ein Wasserstoffatom, eine Niederalkylgruppe oder eine Aralkylgruppe ist, die mindestens einen Substituenten haben kann, R^2, R^3, R^4 und R^5 unabhängig voneinander ein Wasserstoffatom, eine Niederalkylgruppe, eine Arylgruppe, die mindestens einen Substituenten haben kann, oder eine Aralkylgruppe, die einen Substituenten haben kann, darstellen, mit der Maßgabe, dass wenn R^4 und R^5 verschieden sind, R^1 und R^5 zusammen eine Niederalkylengruppe bilden können oder dass R^3 und R^4 zusammen eine Niederalkylengruppe bilden können, die gegebenenfalls einen Substituenten haben kann oder an die ein Benzolring kondensiert ist, und * für ein asymmetrisches Kohlenstoffatom steht, und einem Borhydrid erhalten wird; oder die aus dem optisch aktiven β-Aminoalkohol (I), einem Metallboranat und einer Säure erhalten wird, wobei die Menge des optisch aktiven β-Aminoalkohols (I) im Bereich von 0,005 bis 0,5 Mol pro einem Mol des prochiralen Ketons liegt, und
ii) einem optisch aktiven Oxaza-borolidin der Formel (II):



(II)

in der R^1, R^2, R^3, R^4, R^5 und * die vorstehende Bedeutung haben und R^6 ein Wasserstoffatom, ein Halogenatom, eine Alkylgruppe, die durch mindestens ein Halogenatom substituiert sein kann, eine Arylgruppe, die mindestens einen Substituenten haben kann, oder eine Aralkylgruppe, die mindestens einen Substituenten haben kann, ist, und

(2) ein Metallboranat.

2. Verfahren nach Patentanspruch 1, in dem ein Gemisch aus dem prochiralen Keton und der Säure mit dem Gemisch aus der Boranverbindung und dem Metallboranat umgesetzt wird.

3. Verfahren nach Patentanspruch 1, in dem das prochirale Keton und die Säure dem Gemisch aus der Boranverbindung und dem Metallboranat separat zugefügt werden.

4. Verfahren nach einem der Patentansprüche 1 bis 3, in dem eine Menge des optisch aktiven β-Aminoalkohols (I) in dem Gemisch aus der Boranverbindung und dem Metallboranat 0,01 bis 0,5 Mol pro einem Mol des prochiralen Ketons beträgt.

5. Verfahren nach einem der Patentansprüche 1 bis 4, in dem eine Menge des Metallboranats in dem Gemisch aus der Boranverbindung und dem Metallboranat 0,3 bis 3 Mol pro einem Mol des prochiralen Ketons beträgt.

6. Verfahren nach einem der Patentansprüche 1 bis 5, in dem das prochirale Keton ein Keton der folgenden Formel ist:

$$R^7\text{-CO-}R^8 \qquad \text{(VII)}$$

in der R^7 und R^8 verschieden sind und eine Alkylgruppe, die einen Substituenten haben kann, eine Arylgruppe, die einen Substituenten haben kann, oder eine Aralkylgruppe, die einen Substituenten haben kann, darstellen, oder R^7 und R^8 zusammen mit einem Kohlenstoffatom der Carbonylgruppe einen Ring oder einen kondensierten Ring, der gegebenenfalls ein Heteroatom umfasst, bilden, und der hergestellte optisch aktive Alkohol ein optisch aktiver Alkohol der Formel (VIII):

$$R^7\text{-C*H(OH)-}R^8 \qquad \text{(VIII)}$$

ist, in der R^7 und R^8 die vorstehende Bedeutung haben und * für ein asymmetrisches Kohlenstoffatom steht.

7. Verfahren nach Patentanspruch 6, in dem R^7 und R^8 Gruppen sind, ausgewählt aus der Gruppe bestehend aus einer Alkylgruppe, die einen Substituenten haben kann, und einer Arylgruppe, die einen Substituenten haben kann.

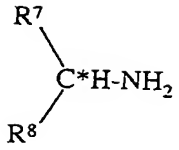
8. Verfahren nach Patentanspruch 7, in dem R^7 und R^8 Gruppen sind, ausgewählt aus der Gruppe bestehend aus Alkylgruppen, halogenierten Alkylgruppen, Arylgruppen, Halogen-Arylgruppen, alkoxyalkyl-substituierten Arylgruppen und aralkyloxy-substituierten Arylgruppen.

9. Verfahren nach einem der Patentansprüche 1 bis 8, in dem die mit dem prochiralen Keton zu verwendende Säure mindestens eine Säure, ausgewählt aus der Gruppe bestehend aus Brønsted-Säuren und Lewis-Säuren, ist.

10. Verfahren nach Patentanspruch 1, in dem ein Gemisch aus dem prochiralen Keton und der Säure mit dem Gemisch aus dem optisch aktiven Oxaza-borolidin und dem Metallboranat umgesetzt wird.

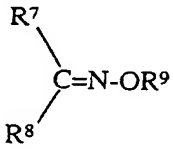
11. Verfahren nach Patentanspruch 1, in dem das prochirale Keton und die Säure dem Gemisch aus dem optisch aktiven Oxaza-borolidin und dem Metallboranat separat zugefügt werden.

12. Verfahren zur Herstellung eines optisch aktiven Amins der Formel (III):



(III)

in der R^7 und R^8 verschieden sind und eine Alkylgruppe, die mindestens einen Substituenten haben kann, eine Arylgruppe, die mindestens einen Substituenten haben kann, oder eine Aralkylgruppe, die mindestens einen Substituenten haben kann, darstellen, oder R^7 und R^8 zusammen mit dem an die Aminogruppe gebundenen Kohlenstoffatom einen Ring oder einen kondensierten Ring, der ein Heteroatom umfassen kann, bilden, und * die vorstehende Bedeutung hat, umfassend das Umsetzen eines Oximderivats der Formel (IV):



(IV)

in der R^7 und R^8 die vorstehende Bedeutung haben und R^9 eine Alkylgruppe, eine Aralkylgruppe oder eine durch Alkyl substituierte Silylgruppe ist, und einer Säure mit einem Gemisch, umfassend:

(1) eine borhaltige Verbindung, ausgewählt aus der Gruppe bestehend aus

i) einer Boranverbindung, erhalten aus einem optisch aktiven β-Aminoalkohol der Formel (I), mit der in Patentanspruch 1 angegebenen Bedeutung, und einem Borhydrid, oder erhalten aus dem optisch aktiven β-Aminoalkohol (I), einem Metallboranat und einer Säure, wobei die Menge des optisch aktiven β-Aminoalkohols (I) 0,01 bis 0,9 Mol pro einem Mol des Oximderivats (IV) beträgt, und
ii) einem optisch aktiven Oxaza-borolidin der Formel (II) mit der in Patentanspruch 1 angegebenen Bedeutung, und

(2) ein Metallboranat.

13. Verfahren nach Patentanspruch 12, in dem das Oximderivat (IV) eine syn-Form, eine anti-Form oder eine Mischung davon, die reich an einer von diesen Formen ist, hat.

14. Verfahren nach Patentanspruch 12, in dem ein Gemisch aus dem Oximderivat und der Säure mit dem Gemisch aus der Boranverbindung und dem Metallboranat umgesetzt wird.

15. Verfahren nach Patentanspruch 12, in dem das Oximderivat und die Säure dem Gemisch aus der Boranverbindung und dem Metallboranat separat zugefügt werden.

16. Verfahren nach Patentanspruch 12, in dem ein Gemisch aus dem Oximderivat und der Säure mit dem Gemisch aus dem optisch aktiven Oxaza-borolidin und dem Metallboranat umgesetzt wird.

17. Verfahren nach Patentanspruch 12, in dem das Oximderivat und die Säure dem Gemisch aus dem optisch aktiven Oxaza-borolidin und dem Metallboranat separat zugefügt werden.

18. Verfahren nach einem der Patentansprüche 12 bis 17, in dem R^7 und R^8 Gruppen sind, ausgewählt aus der Gruppe bestehend aus einer Alkylgruppe, die einen Substituenten haben kann, und einer Arylgruppe, die einen Substituenten haben kann.

19. Verfahren nach Patentanspruch 18, in dem R^7 und R^8 Gruppen sind, ausgewählt aus der Gruppe bestehend aus Alkylgruppen, halogenierten Alkylgruppen, Arylgruppen, Halogen-Arylgruppen, alkoxyalkyl-substituierten Arylgruppen und aralkyloxy-substituierten Arylgruppen.

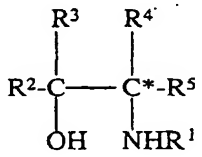
20. Verfahren nach einem der Patentansprüche 12 bis 19, in dem die zusammen mit dem Oximderivat (IV) zu verwendende Säure mindestens eine Säure ausgewählt aus der Gruppe bestehend aus Brønsted-Säuren und Lewis-Säuren, ist.

Revendications

1. Procédé pour la préparation d'un alcool optiquement actif comprenant la réaction d'une cétone prochirale correspondant à l'alcool optiquement actif et d'un acide avec un mélange qui comprend

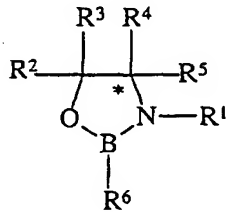
(1) un composé contenant du bore choisi parmi

i) un composé borane qui est obtenu à partir d'un β-aminoalcool optiquement actif de la formule (I):



(I)

où R^1 est un atome d'hydrogène, un groupe alkyle inférieur ou un groupe aralkyle qui peut présenter au moins un substituant, R^2, R^3, R^4 et R^5 représentent indépendamment un atome d'hydrogène, un groupe alkyle inférieur, un groupe aryle qui peut présenter au moins un substituant ou un groupe aralkyle qui peut présenter un substituant, à condition que R^4 et R^5 sont différents, que R^1 et R^5 peuvent former ensemble un groupe alkylène inférieur ou que R^3 et R^4 peuvent former ensemble un groupe alkylène inférieur qui peut présenter facultativement un substituant ou avec lequel un cycle benzène est condensé, et * représente un atome de carbone asymétrique, et d'un hydrure de bore ; ou obtenu à partir dudit β-aminoalcool optiquement actif (I), d'un borohydrure de métal et d'un acide, dans lequel la quantité du β-aminoalcool optiquement actif (I) est comprise entre 0,005 et 0,5 mol par mole de la cétone prochirale, et
ii) une oxazaborolidine optiquement active de la formule (II) :



(II)

où R^1, R^2, R^3, R^4, R^5 et * sont identiques à ceux définis ci-dessus et R^6 est un atome d'hydrogène, un atome d'halogène, un groupe alkyle qui peut être substitué par au moins un atome d'halogène, un groupe aryle qui peut présenter au moins un substituant ou un groupe aralkyle qui peut présenter au moins un substituant, et

(2) un borohydrure de métal.

2. Procédé selon la revendication 1, dans lequel un mélange de ladite cétone prochirale et dudit acide réagit avec ledit mélange du composé borane et du borohydrure de métal.

3. Procédé selon la revendication 1, dans lequel ladite cétone prochirale et ledit acide sont ajoutés audit mélange

du composé borane et du borohydrure de métal séparément.

4. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel une quantité dudit β-aminoalcool optiquement actif (I) dans le mélange du composé borane et du borohydrure de métal est comprise entre 0,01 et 0,5 mol par mole de ladite cétone prochirale.

5. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel une quantité dudit borohydrure de métal dans le mélange du composé borane et du borohydrure de métal est comprise entre 0,3 et 3 mol par mole de ladite cétone prochirale.

6. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel ladite cétone prochirale est une cétone de la formule :

$$R^7\text{-CO-}R^8 \qquad \text{(VII)}$$

où R^7 et R^8 sont différents et représentent un groupe alkyle qui peut présenter un substituant, un groupe aryle qui peut présenter un substituant ou un groupe aralkyle qui présenter un substituant, ou R^7 et R^8 forment ensemble avec un atome de carbone du groupe carbonyle un cycle ou un cycle condensé présentant facultativement un hétéroatome et l'alcool optiquement actif preparé est un alcool optiquement actif de la formule (VIII) :

$$R^7\text{-C*H(OH)-}R^8 \qquad \text{(VIII)}$$

où R^7 et R^8 sont identiques à ceux définis ci-dessus et * représente un atome de carbone asymétrique.

7. Procédé selon la revendication 6, dans lequel R^7 et R^8 sont des groupes choisis parmi un groupe alkyle qui peut présenter un substituant et un groupe aryle qui peut présenter un substituant.

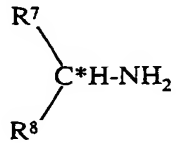
8. Procédé selon la revendication 7, dans lequel R^7 et R^8 sont des groupes choisis parmi des groupes alkyle, des groupes alkyle halogénés, des groupes aryle, des groupes haloaryle, des groupes aryle alcoxyalkyle-substitués et des groupes aryle aralkyloxy-substitués.

9. Procédé selon l'une quelconque des revendications 1 à 8, dans lequel le dit acide à utiliser avec la dite cétone prochirale est au moins un acide choisi parmi les acides de Brønsted et les acides de Lewis.

10. Procédé selon la revendication 1, dans lequel un mélange de ladite cétone prochirale et dudit acide réagit avec ledit mélange de l'oxazaborolidine optiquement active et du borohydrure de métal.

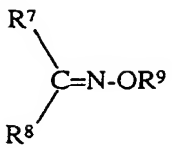
11. Procédé selon la revendication 1, dans lequel ladite cétone prochirale et ledit acide sont ajoutés audit mélange de l'oxazaborolidine optiquement active et du borohydrure de métal séparément.

12. Procédé pour la préparation d'une amine optiquement active de la formule (III):



(III)

où R^7 et R^8 sont différents et représentent un groupe alkyle qui peut présenter au moins un substituant, un groupe aryle qui peut présenter au moins un substituant ou un groupe aralkyle qui peut présenter au moins un substituant, ou R^7 et R^8 forment ensemble avec l'atome de carbone lié au groupe amino un cycle ou un cycle condensé qui peut présenter un hétéroatome, et * est identique à celui défini ci-dessus
comprenant la réaction d'un dérivé d'oxime de la formule (IV) :



(IV)

où R^7 et R^8 sont identiques à ceux définis ci-dessus, et R^9 est un groupe alkyle, un groupe aralkyle ou un groupe silyle alkyle-substitué et d'un acide avec un mélange qui comprend

(1) un composé contenant du bore choisi parmi

i) un composé borane qui est obtenu à partir d'un β-aminoalcool optiquement actif de la formule (I) comme défini dans la revendication 1 et d'un hydrure de bore, ou obtenu à partir dudit β-aminoalcool optiquement actif (I), d'un borohydrure de métal et d'un acide, dans lequel la quantité du β-aminoalcool optiquement actif (I) est comprise entre 0,01 et 0,9 mol par mole du dérivé d'oxime (IV),
ii) une oxazaborolidine optiquement active de la formule (II) comme défini dans la revendication 1

et (2) un borohydrure de métal.

13. Procédé selon la revendication 12, dans lequel ledit dérivé d'oxime (IV) est une forme syn, une forme anti ou un mélange de celles-ci qui est riche en l'une d'entre elles.

14. Procédé selon la revendication 12, dans lequel un mélange dudit dérivé d'oxime et dudit acide réagit avec ledit mélange du composé borane et du borohydrure de métal.

15. Procédé selon la revendication 12, dans lequel ledit dérivé d'oxime et ledit acide sont ajoutés audit mélange du composé borane et du borohydrure de métal séparément.

16. Procédé selon la revendication 12, dans lequel un mélange dudit dérivé d'oxime et dudit acide réagit avec ledit mélange de l'oxazaborolidine optiquement active et du borohydrure de métal.

17. Procédé selon la revendication 12, dans lequel ledit dérivé d'oxime et ledit acide sont ajoutés audit mélange de l'oxazaborolidine optiquement active et du borohydrure de métal séparément.

18. Procédé selon l'une quelconque des revendications 12 à 17, dans lequel R^7 et R^8 sont des groupes choisis parmi un groupe alkyle qui peut présenter un substituant et un groupe aryle qui peut présenter un substituant.

19. Procédé selon la revendication 18, dans lequel R^7 et R^8 sont des groupes choisis parmi des groupes alkyle, des groupes alkyle halogénés, des groupes haloaryle, des groupes aryle alcoxyalkyle-substitués et des groupes aryle aralkyloxy-substitués.

20. Procédé selon l'une quelconque des revendications 12 à 19, dans lequel ledit acide à utiliser avec ledit dérivé d'oxime (IV) est au moins un acide choisi parmi les acides de Brønsted et les acides de Lewis.